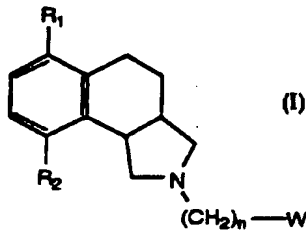


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 487/02, A61K 31/505, C07D 495/02, 475/02, 487/00 // (C07D 487/00, 239:00, 209:00) (C07D 495/02, 333:00, 239:00, 209:00) (C07D 487/02, 239:00, 209:00, 209:00)</p>	<p>A1</p>	<p>(11) International Publication Number: WO 96/22991 (43) International Publication Date: 1 August 1996 (01.08.96)</p>
<p>(21) International Application Number: PCT/US96/00178 (22) International Filing Date: 11 January 1996 (11.01.96) (30) Priority Data: 08/379,823 27 January 1995 (27.01.95) US 08/465,476 5 June 1995 (05.06.95) US (71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US).</p>		<p>(72) Inventors: MEYER, Michael, D.; 25151 Amanda Court, Lake Villa, IL 60046 (US). ALTENBACH, Robert, J.; 7405 North Oketo, Chicago, IL 60631 (US). BASHA, Fatima, Z.; 41 East Heron Drive, Lake Forest, IL 60045 (US). CARROLL, William, A.; 2514 Prairie Avenue, #3B, Evanston, IL 60201 (US). DRIZIN, Irene; 16764 West Cherrywood Lane, Wadsworth, IL 60083 (US). KERWIN, James, F., Jr.; 301 West Willowby Court, Grayslake, IL 60030 (US). LEBOLD, Suzanne, A.; 2007 North Sedgwick, #605, Chicago, IL 60614 (US). LEE, Edmund, L.; 275 Hidden Creek Road, Lake Zurich, IL 60047 (US). PRATT, John, K.; 8210 61st Avenue, Kenosha, WI 53142 (US). SIPPY, Kevin, B.; 678 Federal Parkway, Lindenhurst, IL 60046 (US). TIETJE, Karin, R.; 485 Killarney Pass Circle, Mundelein, IL 60060 (US). YAMAMOTO, Diane, M.; 1628 Dolcetto Lane, Gurnee, IL 60031 (US). (74) Agents: JANSSEN, Jerry, F. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, 100 Abbott Park Road, Abbott Park, IL 60064-3500 (US). (81) Designated States: AU, CA, JP, KR, MX, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: BICYCLIC SUBSTITUTED HEXAHYDROBENZ[E]ISOINDOLE ALPHA-1- ADRENERGIC ANTAGONISTS</p> <p>(57) Abstract</p> <p>The present invention relates to a compound of formula (I) and the pharmaceutically acceptable salts thereof wherein W is a bicyclic heterocyclic ring system. The compounds are α-1 adrenergic antagonists and are useful in the treatment of BPH; also disclosed are α-1 antagonist compositions and a method for antagonizing α-1 receptors and treating BPH.</p> <div style="text-align: center;">  <p>(I)</p> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**Bicyclic Substituted Hexahydrobenz[e]isoindole
Alpha-1-Adrenergic Antagonists**

Cross-Reference to Related Applications

5 This application is a continuation-in-part of co-pending application Serial No. 08/379,823 filed January 27, 1995.

Technical Field

10 The present invention relates to novel organic compounds and compositions which are alpha-1 (α -1) adrenoreceptor antagonists, processes for making such compounds, synthetic intermediates employed in these processes, and a method for inhibiting alpha-1 adrenoceptors and treating benign prostatic hyperplasia (BPH), also called benign prostatic hypertrophy.

Background of the Invention

15 Adrenergic neurons play a major role in the innervation of heart, blood vessel and smooth muscle tissue. Compounds capable of interacting with adrenoceptor sites within adrenergic nerves can initiate a variety of physiological responses, including vasoconstriction, vasodilation, and increased or decreased
20 heart rate (chronotropic), contractility (inotropic) and metabolic activity. In the past, various adrenergic compounds have been employed to affect these and other physiological responses. However, many adrenergic compounds do not possess significant selectivity to enable desirable interactions with adrenergic receptor sites. That is, these adrenergic compounds do not demonstrate a high degree of specificity
25 for differing receptor types within adrenergic neurons in order to obtain a desired physiological response separate from other possible, and perhaps less desirable, responses of the system.

 Benign prostatic hyperplasia (BPH) is a condition which develops in middle-aged and elderly males and refers to the benign overgrowth of the stromal and
30 epithelial elements of the prostate associated with aging. Symptoms of BPH include increased frequency of urination, nocturia, a weak urine stream and hesitancy or delay in starting the urine flow. Chronic consequences of BPH can include hypertrophy of bladder smooth muscle, a decompensated bladder and an increased incidence of urinary tract infection.

Typically, BPH begins at an age in the mid-fifties and is the most common cause of urinary tract problems of men of this age. BPH is apparently rare in men prior to age 40, but at age 60, approximately 50% of men have histological evidence of BPH. The prevalence of BPH continues to increase with age until, at age 80, approximately 80% of men have pathological evidence of BPH.

Although prostatic hyperplasia is a common finding in older men, the presence of urinary symptoms is the essential feature that distinguishes simple anatomic enlargement of the prostate from prostatism, which is the clinical syndrome whereby the patient experiences significant obstruction of urinary flow. It is not uncommon in older men to have a palpably enlarged prostate without showing the symptoms of prostatism. From the patient's perspective, however, the incidence and progression of urinary symptoms are more important than the mere presence of an enlarged prostate.

The discovery in the 1970's (M. Caine, *et al.*, *Brit. J. Urol.*, 47: 193-202 (1975)) of large numbers of alpha-adrenergic receptors in the smooth muscle of the prostatic capsule and bladder neck led to the conclusion that there is both a static and a dynamic component to bladder outlet obstruction associated with BPH. The static component derives from the progressive hyperplasia of the prostate with aging, leading to urethral narrowing which causes symptoms of urinary obstruction. Superimposed on this essentially mechanical problem is the variable degree of smooth muscle contraction controlled by the sympathetic nervous system and which is affected by factors such as stress, cold and sympathomimetic drugs. It is this dynamic component which explains the often rapid fluctuations in symptoms observed in patients with prostatism.

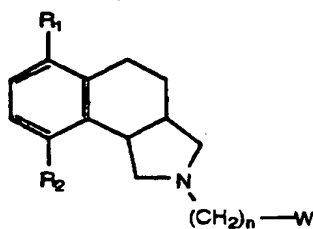
The currently most effective treatment for BPH is the surgical procedure of transurethral resection of the prostate (TURP). Since it removes the obstructing tissue (C. Chapple, *Br. Med. Journal* 304: 1198-1199 (1992)) it is a treatment which is directed to the static and dynamic components of BPH. However, this surgical treatment is associated with rates of mortality (1%) and adverse event (incontinence 2-4%, infection 5-10%, and impotence 5-10%). A non-invasive alternative treatment would thus be highly desirable.

The incidental clinical observation that urinary incontinence developed in women during antihypertensive treatment with prazosin (T. Thien, K. P. Delacre, F. M. J. Debruyne, R. A. P. Koene, *Br. Med. Journal*, 622-623 (1978)) and the experimental work of Caine (*op cit.*) contributed to the recognition of the potential role of selective α -1 adrenoceptor blockade in diseases of the lower urinary tract.

Subsequent studies by several groups have documented the functional role of α -1 adrenoceptors relative to α -2 adrenoceptors in the stromal compartment of the prostate, thereby providing a putative molecular basis for the use of specific α -1 adrenoceptor blockers in the non-surgical management of BPH (C. R. Chapple, M. L. Aubry, S. James, M. Greengrass, G. Burnstock, R. T. Turner-Warwick, *Br. J. Urol.* **63**: 487-496 (1989)). Clinical efficacy of α -1 antagonists in BPH has been demonstrated with several non-selective α -1 blockers, including terazosin (Hytrin™), prazosin, and doxazosin. Treatment periods as short as two to four weeks with α -1 adrenoceptor blockers have shown objective improvements in the mean and maximum urinary flow rates (14-96%) with subjective improvements in patients' symptom scores (R. A. Janknegt, C. R. Chapple, *Eur. Urol.* **24**: 319-326 (1993)). Longer term studies with terazosin, indoramin, prazosin, and doxazosin have similarly demonstrated significant improvements in urinary flow rates and subjective symptom scores (R. A. Janknegt, op. cit., H. Lepor, G. Knapp-Maloney, *J. Urol.* **145**: 263A (1991), W. Chow, D. Hahn, D. Sandhu, *Br. J. Urol.* **65**: 36-38 (1990) and C. R. Chapple, T. J. Christmas, E. J. G. Milroy, *Urol. Int.* **45**: 47-55 (1990)). However, these agents possess similar dose limiting side effects: hypotension, dizziness, and muscle fatigue. There thus exists a need for a "uroselective" α -1 antagonist with reduced side effect liabilities.

Summary of the Invention

In its principle embodiment, the present invention provides certain hexahydro-[1H]-benz[e]isoindole compounds of the formula I:

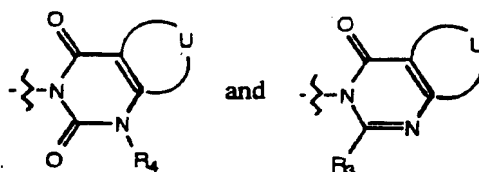


or a pharmaceutically acceptable salt thereof wherein n is an integer from 2 to 6.

R_1 and R_2 are independently selected from the group consisting of hydrogen, alkyl of one to six carbon atom, alkoxy of one to six carbon atoms, hydroxy, halo, carboxy, and alkoxycarbonyl of two to eight carbon atoms.

4

W is selected from the group consisting of

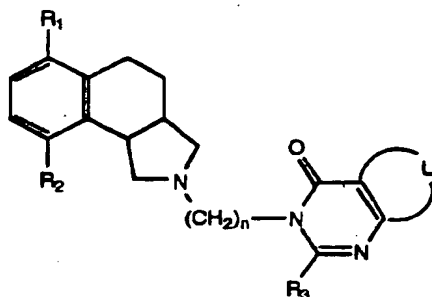


- 5 wherein R₃ is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, unsubstituted phenyl and phenyl substituted with alkyl of one to six carbon atoms, and R₄ is hydrogen or alkyl of one to six carbon atoms.

- U, taken together with the carbon atoms to which it is attached forms a ring selected from the group consisting of (a) an unsubstituted or substituted five
 10 membered ring having four carbon atoms, two double bonds and one heteroatom selected from the group consisting of -N(R₅)-, -O- and -S- wherein R₅ is hydrogen or alkyl of one to six carbon atoms and the ring substituent is selected from the group consisting of alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six
 15 carbon atoms; (b) an unsubstituted or substituted five membered ring having three carbon atoms, two double bonds and two heteroatoms selected from the group consisting of two nitrogen atoms, one oxygen atom and one nitrogen atom, and one sulfur atom and one nitrogen atom wherein the ring substituent is selected from the group consisting of alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro,
 20 carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms; (c) a benzene ring which is unsubstituted or substituted with a substituent selected from the group consisting of alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms methylenedioxy and ethylenedioxy; and
 25 (d) an unsubstituted or substituted six membered ring having one to three double bonds and one or two nitrogen atoms, wherein the ring substituent is selected from the group consisting of alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms.

5

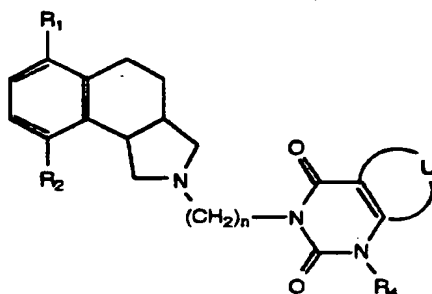
In one embodiment, the present invention provides a compound of the formula



(II)

wherein R_1 , R_2 , n , R_3 and U are as previously defined.

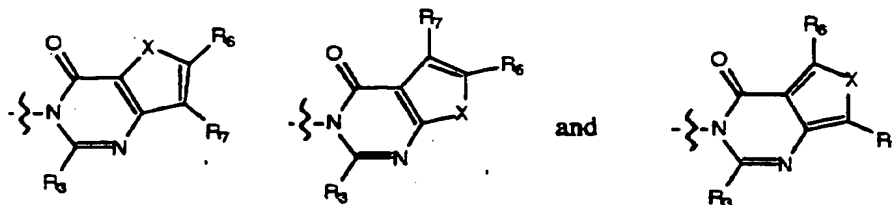
In another embodiment, the present invention provides a compound of the formula



(III)

wherein R_1 , R_2 , n , R_4 and U are as previously defined.

Yet another embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of

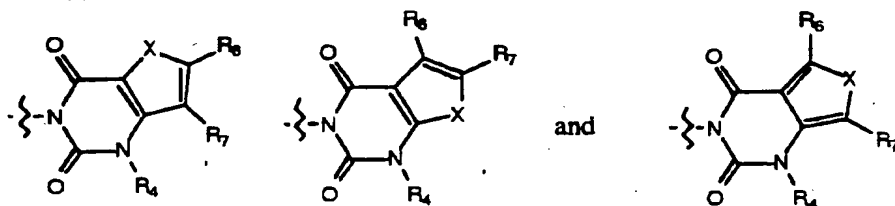


wherein X is selected from the group consisting of $-N(R_5)-$, $-O-$ and $-S-$ wherein R_5 is hydrogen or alkyl of one to six carbon atoms, R_6 and R_7 are the same or different and are independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to

6

eight carbon atoms and alkoxy of one to six carbon atoms, and R_3 is as previously defined.

In yet another embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of



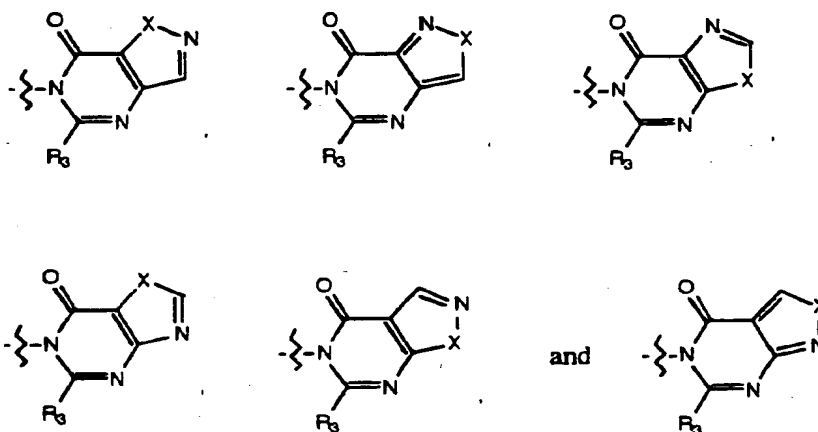
5

wherein X is selected from the group consisting of $-N(R_5)-$, $-O-$ and $-S-$ wherein R_5 is hydrogen or alkyl of one to six carbon atoms, R_6 and R_7 are the same or different and are independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxy carbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms, and R_4 is as previously defined.

10

Another embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of

15

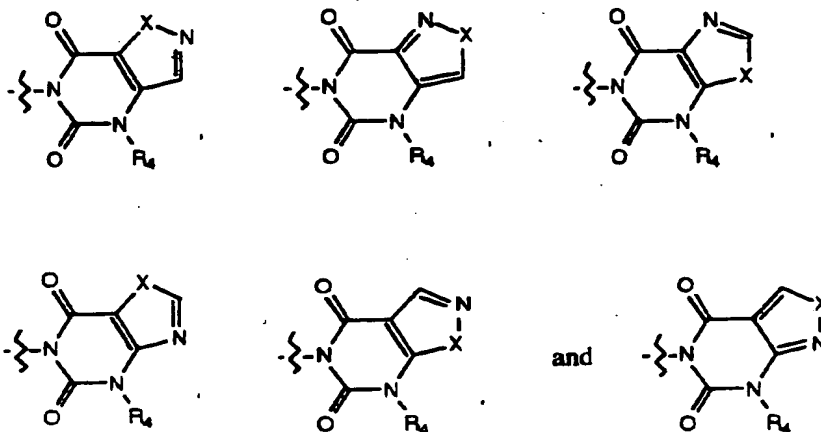


wherein X is selected from the group consisting of $-N(R_5)-$, $-O-$ and $-S-$ wherein R_5 is hydrogen or alkyl of one to six carbon atoms and R_3 is as previously defined.

20

7

Another embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of

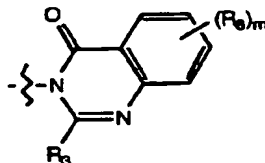


5

wherein X is selected from the group consisting of $-N(R_5)-$, $-O-$ and $-S-$ wherein R_5 is hydrogen or alkyl of one to six carbon atoms and R_4 is as previously defined.

Yet another embodiment of the present invention provides a compound of formula (I) wherein W is

10



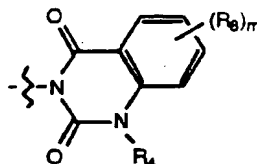
wherein m is selected from 1, 2 and 3 and, when m is 2 or 3, R_8 at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms, alkoxy of one to six carbon atoms and, when m is 2, methylenedioxy and ethylenedioxy, and R_3 is as previously defined.

15

20

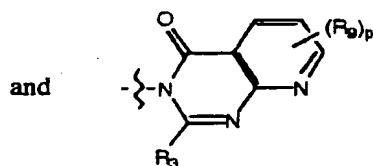
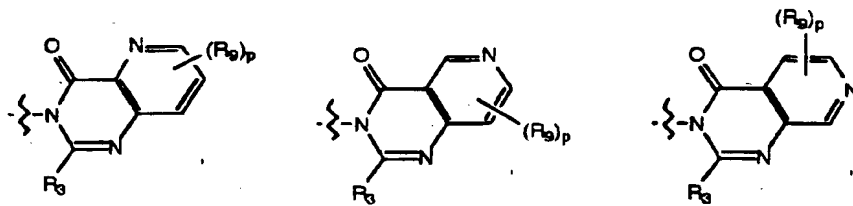
8

Another embodiment of the present invention provides a compound of formula (I) wherein W is



wherein m is selected from 1, 2 and 3 and, when m is 2 or 3, R₈ at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms, alkoxy of one to six carbon atoms and, when m is 2, methylenedioxy and ethylenedioxy, and R₄ is as previously defined.

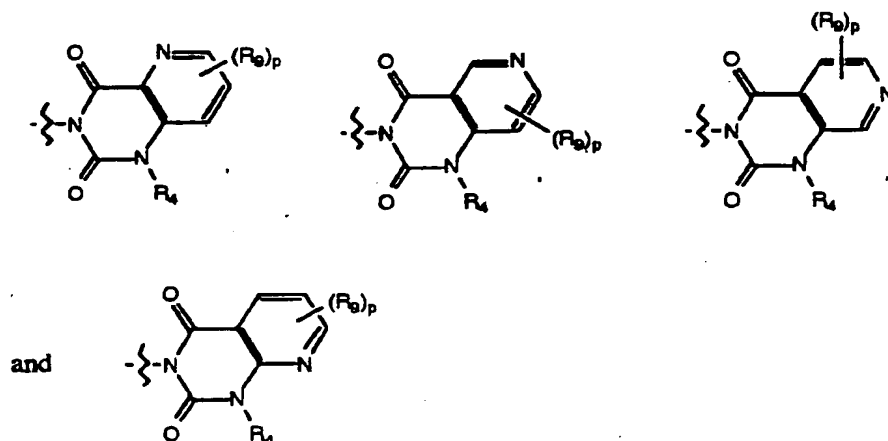
In yet another embodiment, the present invention provides a compound of formula (I) wherein W is selected from the group consisting of



wherein p is selected from 1 and 2 and, when p is 2, R₉ at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms, and R₃ is as previously defined.

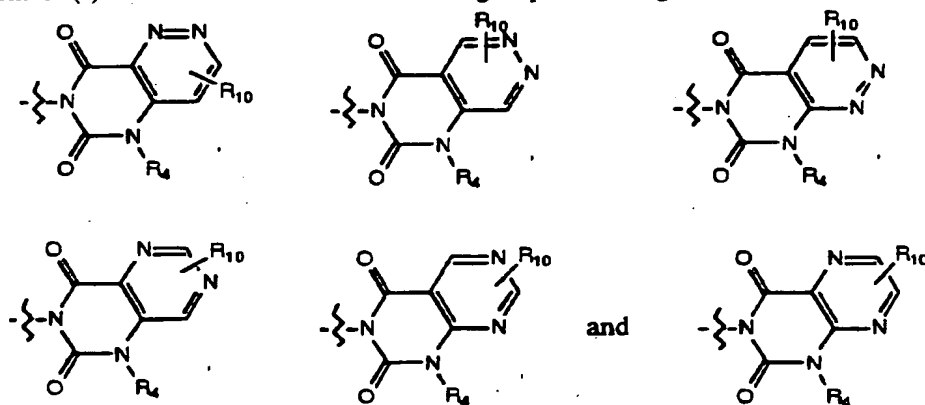
9

Another embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of



5 wherein p is selected from 1 and 2 and, when p is 2, R_9 at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms, and alkoxy of one to six carbon atoms, and R_4 is as previously defined.

10 Another embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of



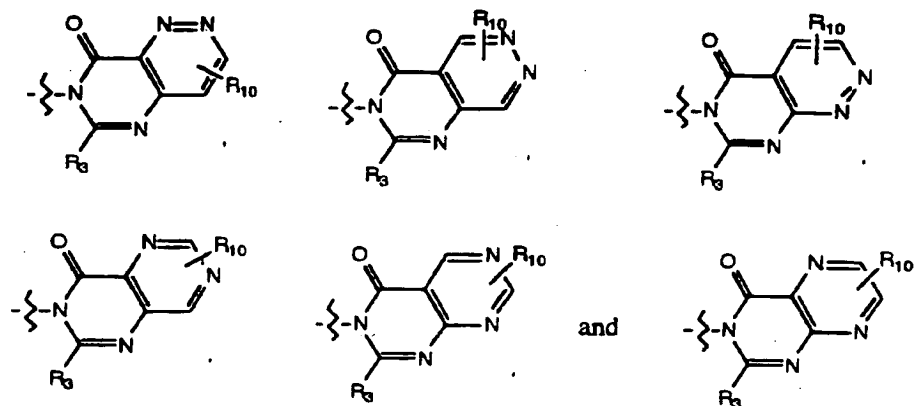
15 wherein R_{10} is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight

10

carbon atoms and alkoxy of one to six carbon atoms and R_4 is as previously defined.

Another embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of

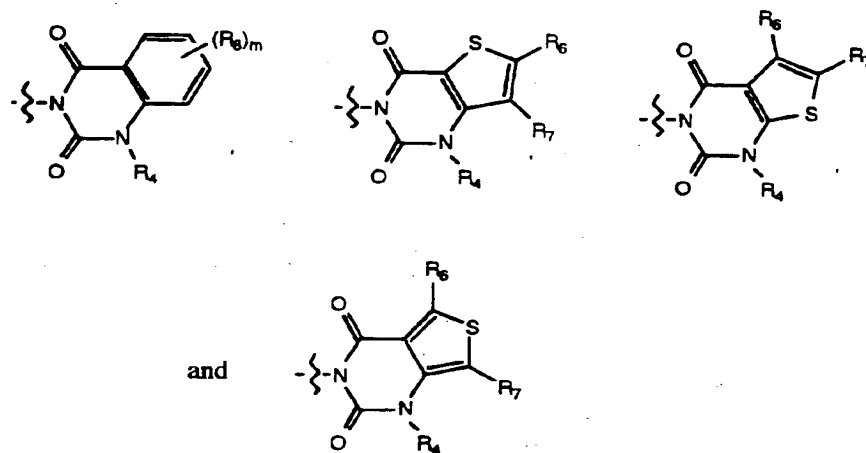
5



10

wherein R_{10} is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms, and alkoxy of one to six carbon atoms and R_3 is as previously defined.

A preferred embodiment of the present invention provides a compound of formula (I) wherein W is selected from the group consisting of

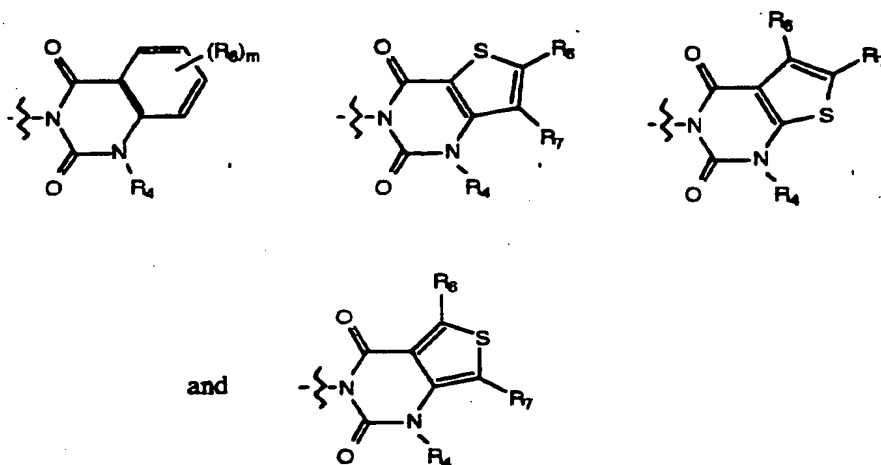


15

11

wherein R_1 , R_2 , n , m , R_4 , R_6 , R_7 and R_8 are as previously defined.

A more preferred embodiment of the present invention is a compound of formula (I) wherein one of R_1 and R_2 is alkoxy of one to six carbon atoms and the other one is hydrogen, n is selected from an integer from 2 to 4 and W is selected from the group consisting of



wherein R_1 , R_2 , n , m , R_4 , R_6 , R_7 and R_8 are as previously defined.

10 The present invention also relates to pharmaceutical compositions which comprise a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

The invention further relates to a method of antagonizing α -1 receptors in a host mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

15 The invention still further relates to a method of treating BPH in a host mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

Detailed Description of the Invention

20 As used throughout this specification and the appended claims, the following terms have the meaning specified.

The term "alkyl" as used herein refer to straight or branched chain alkyl radicals including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkoxy" as used herein refers to an alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, isopropoxy, tert-butoxy, and the like.

5 The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like.

10 The term "ethylenedioxy" as used herein refers to $-O-CH_2-CH_2-O-$ which when attached to two adjacent positions on a benzene ring forms a six-membered ring.

The term "methylenedioxy" as used herein refers to $-O-CH_2-O-$ which when attached to two adjacent positions on a benzene ring forms a 5-membered ring.

15 By "pharmaceutically acceptable salt" is meant those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts are well known in the art. For example, S.M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharm. Sciences*, 66: 1-19 (1977). The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, 25 aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2- 30 naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, *p*-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, 35 diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and

phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine.

Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

Asymmetric centers may exist in the compounds of the present invention. The present invention contemplates the various stereoisomers and mixtures thereof. Starting compounds of particular stereochemistry are either commercially available or are made by the methods detailed below and resolved by techniques well known in the art of organic chemistry.

Representative examples of compounds falling within the scope of this invention include:

- 3-[2-(*cis*-9-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-[1H,3H]-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-9-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-methylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5-phenyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride;

- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-phenyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[3,4-d]pyrimidine-2,4(1H,3H)-dione;
- 5 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-8-methoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-chloro-quinazoline-2,4(1H,3H)-dione;
- 10 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5-methyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 15 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbomethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-fluoro-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-nitro-quinazoline-2,4(1H,3H)-dione;
- 20 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7,8-trimethoxy-quinazoline-2,4(1H,3H)-dione;
- 25 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-8-methyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,8-dimethyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 30 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-pyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5-chloro-quinazoline-2,4(1H,3H)-dione;
- 35 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-pyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione;

15

- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-fluoro-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-quinazoline-2,4(1H,3H)-dione;
- 5 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-pyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-1H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione;
- 10 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-phenylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 15 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-phenylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-4(3H)-one;
- 20 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-quinazoline-4(3H)-one;
- 3-[2-(*cis*-6-hydroxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-quinazoline-2(1H)-one;
- 25 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-ethylenedioxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 30 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 35 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-4(3H)-one;

- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-4(3H)-one;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-quinazoline-2(1H)-one;
- 5 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-quinazoline-4(3H)-one;
- 2-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1,2,3,4-tetrahydroisoquinolin-1,3-dione;
- 2-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline;
- 10 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-2,4-pteridinedione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-(3,4-dimethoxyphenyl)-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 15 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-chlorothieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-6-dimethylaminocarbonyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 20 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]oxazolo[5,4-d]pyrimidine-5,7(4H,6H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-amino-oxazolo[5,4-d]pyrimidin-5(6H)-one;
- 25 1-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-3,9-dimethyl-[1H]-purine-2,6-dione;
- 1-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-3,7-dimethyl-[7H]-imidazo[4,5-d]pyrimidin-2,6-dione;
- 30 3-[4-(*cis*-9-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)butyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-methoxy-quinazoline-2,4(1H,3H)-dione;
- 35

- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-methylsulfonylamino-quinazoline-2,4(1H,3H)-dione;
- 5 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-ethylenedioxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-hydroxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione;
- 2-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-4-amino-6,7-dimethoxy-quinazoline;
- 10 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-chloro-7-methoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-7-chloro-quinazoline-2,4(1H,3H)-dione;
- 15 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-dimethylaminocarbonyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-cyano-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*trans*-9-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-[1H,3H]-quinazoline-2,4(1H,3H)-dione;
- 20 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-8-methoxy-quinazoline-2,4(1H,3H)-dione;
- 25 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-chloro-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbomethoxy-quinazoline-2,4(1H,3H)-dione;
- 30 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7,8-trimethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methylquinazoline-2,4(1H,3H)-dione;
- 35 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-4(3H)-one;

- 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-ethylenedioxyquinazoline-2,4(1H,3H)-dione;
- 5 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-(*trans*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbamylquinazoline-2,4(1H,3H)-dione;
- 10 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-(*N,N'*-dimethyl)carbamylquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,8-dichloro-7-methoxyquinazoline-2,4(1H,3H)-dione;
- 15 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-chloro-6-methoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-6-chloro-7-methoxyquinazoline-2,4(1H,3H)-dione;
- 20 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5,6-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethylquinazoline-4(3H)-one;
- 25 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-carbomethoxythieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-carbomethoxythieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 30 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5-carboethoxy-1H-pyrrolo[2,3-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-7-phenylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 35

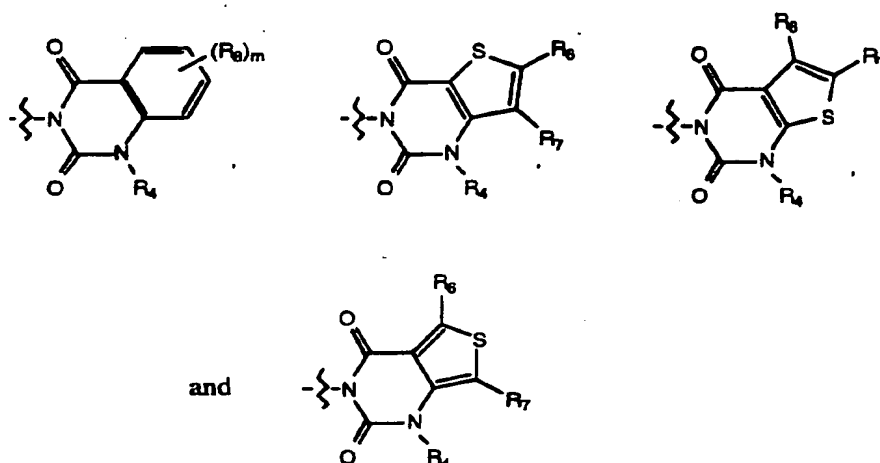
19

- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-7-ethylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 5 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-7-methylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-7-isopropylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 10 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethylquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carboxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carboisopropoxyquinazoline-2,4(1H,3H)-dione;
- 15 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-acetamidoquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-methanesulfonylquinazoline-2,4(1H,3H)-dione;
- 20 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-quinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-(2-methylphenyl)thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 25 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-(2-methoxyphenyl)thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione;
- 30 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-2,4-pteridinedione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-pyrimidino[4,5-d]pyrimidine-2,4(1H,3H)-dione;
- 35 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-7-methoxyquinazoline-2,4(1H,3H)-dione;

- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-(2-methoxyethyl)-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 5 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-4(3H)-one dihydrochloride;
- 10 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethoxyquinazoline-4(3H)-one;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 15 3-[2-((3a*R*,9b*R*)-*cis*-9-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)butyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbomethoxyquinazoline-2,4(1H,3H)-dione;
- 20 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carboisopropoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbopropoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-nitroquinazoline-2,4(1H,3H)-dione;
- 25 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-methoxy-8-methyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-ethoxy-8-methyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethylquinazoline-2,4(1H,3H)-dione;
- 30 3-[2-((3a*R*,9b*R*)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)-*cis*-6-ethoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione; and
- 35 3-[2-((3a*R*,9b*R*)-*cis*-6-ethyl-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione; or a

pharmaceutically acceptable salt thereof.

Preferred compounds are selected from those having formula (I) wherein one of R_1 and R_2 is alkoxy of one to six carbon atoms and the other one is hydrogen, n is selected from an integer from 2 to 4, and W is selected from the group consisting of



wherein m is selected from 1, 2 and 3, R_6 and R_7 are the same or different and are independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxy, alkoxy carbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms, R_8 at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, halo, cyano, nitro, carboxy, alkoxy, alkoxy carbonyl of two to eight carbon atoms, alkoxy of one to six carbon atoms and, when m is two, methylenedioxy and ethylenedioxy, and R_4 is as previously defined is selected from the group consisting of:

- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-8-methoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-chloro-quinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;

- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbomethoxy-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-quinazoline-2,4(1H,3H)-dione;
- 5 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,8-dimethyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-quinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 10 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-ethylenedioxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 15 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-4(H)-one;
- 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-7-methoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-(2-methoxyethyl)-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 20 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione;
- 25 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-4(3H)-one;
- 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethoxyquinazoline-4(3H)-one;
- 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione;
- 30 3-[2-((3aR,9bR)-*cis*-9-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)butyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbomethoxyquinazoline-2,4(1H,3H)-dione;
- 35 3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carboisopropoxyquinazoline-2,4(1H,3H)-dione;

23

- 3-[2-((3aR,9bR)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbopropoxyquinazoline-2,4(1H,3H)-dione;
 3-[2-((3aR,9bR)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-nitroquinazoline-2,4(1H,3H)-dione;
 5 3-[2-((3aR,9bR)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-methoxy-8-methyl-quinazoline-2,4(1H,3H)-dione;
 3-[2-((3aR,9bR)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-ethoxy-8-methyl-quinazoline-2,4(1H,3H)-dione;
 3-[2-((3aR,9bR)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethylquinazoline-2,4(1H,3H)-dione;
 10 3-[2-((3aR,9bR)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-dimethoxyquinazoline-2,4(1H,3H)-dione;
 3-[2-((3aR,9bR)*cis*-6-Ethoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione; and
 15 3-[2-((3aR,9bR)*cis*-6-Ethyl-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
 or a pharmaceutically acceptable salt thereof.

Representative compounds of the present invention were evaluated for their
 20 ability to displace prazosin from its receptor.

In vitro Binding Assays

In the following, for purposes of discussing alpha-1 receptor subtypes, the IUPAC convention of using lower case letters to define molecular clones and upper
 25 case letters to indicate pharmacologically defined receptors has been followed. Moreover, the newly recommended nomenclature for alpha-1 (α_{1a} , α_{1b} , α_{1d}) has been used.

Representative compounds of the invention were evaluated for α -adrenoceptor binding affinity in vitro using [3 H]-prazosin as the radioligand and
 30 three cloned α -1 adrenoceptors expressed in LTK cells: α -1: α -1a (bovine), α -1b (hamster) and α -1d (rat). Additionally, binding affinity against the pharmacologically defined α -1A adrenoceptor (rat submaxillary gland) was measured.

The cDNA clones encoding the α -1 receptors (α -1a, α -1b, and α -1d) were
 35 obtained from TULCO (Triangle Universities Licensing Consortium, Research Triangle Park, NC) and inserted into the eukaryotic expression vector SnaB30. In

this vector, expression of the receptor gene is under the transcriptional control of an SV40 early promoter. Positive drug selection is provided by a neomycin-resistance gene. Mouse fibroblast cells (LTK) were transfected with the α_1 expression plasmids and grown in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum and 30 μ M G418. Stable G418-resistant parental lines were generated, with successful expression of receptor protein monitored using radioligand binding techniques. Stable single cell clones derived from the parental lines were screened in receptor binding assays to identify clones having high receptor density. Roller bottle cultures of the cloned lines were used to provide cell membranes for subsequent receptor binding characterization studies. A cell line containing the SnaB30 vector expressing the human erythropoietin gene served as a negative control.

For receptor binding assays, large scale membrane preparations were utilized in which 6 million cells were seeded into small (450 cm²) Corning tissue culture roller bottles. 200 mL of DMEM containing 10% fetal calf serum and 300 μ M G418 were added to each roller bottle. A 95% air / 5% CO₂ gas mixture (sterile) was injected into each roller bottle prior to sealing. The bottles were then incubated at 37 °C on a roller rack for 5 days. Cells were re-fed with fresh medium after 3 days in culture.

On the fifth day of culture, growth medium was removed from cells grown in roller bottles, and the cells were washed twice with PBS (Sigma, 120 mM NaCl, 2.7 mM KCl, 10 mM Na₂HPO₄-NaH₂PO₄, pH = 7.4). Cells were detached from the roller bottles by incubating for 15 minutes at 37 °C in a Tris-EDTA solution (10 mM Tris, 100 mM NaCl, 1 mM EDTA, pH = 7.4). The cell suspension from each roller bottle was decanted into tared centrifuge tubes and kept on ice. An aliquot of each cell suspension was generally taken for cell counting. Cells were centrifuged at 3000 X G for 5 min at 2-4 °C, washed with PBS and recentrifuged. The supernatant was decanted and the pellet weighed to determine the wet weight of cells. Cells were washed a final time in 40 vol 5 mM Tris-HCl, 5 mM EDTA, pH = 7.7, and centrifuged at 40,000 X G for 10 minutes. Cells were homogenized in 10 mL of 50 mM Tris-HCl, 5 mM EDTA (pH = 7.4) and diluted to 40 mL/tube. Homogenates were centrifuged at 40,000 X G for 10 minutes. The supernatant was decanted and the pellets rehomogenized in 50 mM Tris-HCl (pH = 7.4) and centrifuged as before. The supernatant was decanted and the homogenate resuspended in 6.25 volumes (per gram wet weight) of 50 mM Tris-HCl and aliquots of the pooled homogenates frozen in liquid N₂ and stored at -70 °C until the time of assay. Rat submaxillary

glands were used for α -1A receptors and were prepared essentially as described (Michel, A. D., Loury, D. N. and Whiting, R. L., *Brit. J. Pharmacol.* **98**: 83-889 (1989)).

Receptor binding assays for α -1 receptors were performed essentially as described by Greengrass and Bremner (*Eur. J. Pharmacol.* **55**: 323-326 (1979)). Briefly, plastic BioblocksTM (DBM Scientific, Valencia, CA) were incubated at 25 °C for 50 minutes with 500 μ L of membrane homogenate (diluted with an additional 96 volumes [for cloned receptors, 12 volumes for submaxillary gland] in 50 mM Tris-HCl buffer (pH = 7.7 at the time of assay), 450 μ L of [³H]prazosin (0.2 nM final concentration, 75-85 Ci/mmmole, DuPont-NEN Corp., Boston, MA) and 50 μ L of either water (for total binding) or 10 μ M phentolamine (final concentration, for non-specific binding). Following equilibration, bound radioligand was separated from free on GF/B filters (presoaked in 0.5% polyethyleneimine) using either a Brandel or Packard cell harvester. Radioactivity was determined by standard liquid scintillation techniques. Data were analyzed as previously described (Hancock, A. A., Kyncl, J. J., Martin, Y. C. and DeBernardis, J. F., *J. Receptor Res.* **8**: 23-46 (1988)).

Canine prostate strips were used *in vitro* as previously described (Hieble, J.P., Boyce, A.J. and Caine, M., *Fed. Proc.*, **45**: 2609-2614 (1986)), to determine antagonist potencies against phenylephrine-induced contractions.

The results are shown in Table 1. The results show that the compounds of the invention bind to the α -1 adrenoceptor and show varying degrees of specificity for the α -1a receptor.

Table 1
In Vitro Data for Binding to α -1 Adrenoceptors

Ex. No.	α -1A (Rat) (nM)	α -1b (Hamster) (nM)	α -1a (Bovine) (nM)	α -1d (Rat) (nM)
1	1.012	1.84	0.212	0.893
2	0.847	1.28	0.182	0.707
3	2.468	3.65	0.443	2.381
4	3.704	3.803	1.489	2.681
5	1.392	1.631	0.268	0.919
6	16.588	11.806	2.149	15.92
7	14.912	14.186	2.812	55.718
8	0.481	1.015	0.203	0.517

26

9	0.845	2.273	0.19	1.155
10	0.666	10.601	0.149	3.384
11	0.57	2.708	0.042	0.584
12	1.891	1.038	0.501	1.132
13	0.971	1.982	0.254	0.97
14	0.318	1.936	0.086	2.051
15	1.341	2.48	0.239	1.96
16	8.027	15.407	1.225	2.715
17	1.377	4.952	0.318	1.12
18	1.704	17.385	0.579	5.66
19	0.371	1.4	0.048	0.814
20	2.731	16.279	0.425	2.863
21	1.19	3.31	0.472	1.995
22	2.732	6.471	0.939	2.153
23	0.604	1.017	0.052	0.711
24	1.414	3.103	0.311	1.783
25	0.931	1.622	0.199	0.952
26	0.407	1.326	0.089	1.333
27	4.435	10.576		2.872
28	43.665	66.695	10.098	42.764
29	3.437	9.292	0.978	2.88
30	1.205	2.587	0.483	1.671
31	0.302	0.426	0.124	0.599
32	7.773	11.349	0.139	4.403
33	1.349	24.279		16.595
34	1.275	4.285		2.839
35	47.195	97.372		36.631
36	7.576	11.165		3.378
37	0.021	0.567		0.159
38	0.097	0.341		0.105
39	0.28	6.33		1.401
42	0.277	16.007		7.048
44	7.576	11.165		3.378
46	.115	.699	.058	.362
47	1.345	2.349	.273	.722

48	6.243	19.411	1.265	22.539
49	1.097	3.349	.493	1.387
50	.123	1.082	.079	.771
51	2.426	8.51	.239	4.688
52	1.878	20.477	.542	12.057
53	.908	2.386	.259	.43
54	.28	1.371	.073	.865
55	2.808	11.908	.482	12.604
56	2.078	54.925	.542	46.465
57	2.217	7.564	.477	4.125
58	.634	3.592	.224	3.137
59	11.07	28.623	2.364	12.139
60	1.477	3.372	.23	1.377
61	6.962	10.808	2.003	2.678
62	.967	2.136	.14	2.457
63	.807	4.73	.337	2.242
64	1.095	7.147	.242	1.451
65	.413	2.312	.12	1.502
66	1.071	9.504	.242	2.231
67	.161	1.198	.064	.982
68	1.384	4.073	.138	.73
69	.275	1.645	.056	.774
70	12.991	26.977	3.792	11.079
71	.48	3.881	.102	1.028
72	2.11	10.263	.328	3.33
73	2.788	8.384	.343	2.754
74	.912	3.331	.262	1.204
75	.198	.84	.161	.415
76	.836	1.315	.509	1.278
77	.448	1.987	.106	.976
78	.612	5.756	.333	4.565
79	.666	1.164	.204	.619
80	.091	1.316	.021	.892
81	.037	.662	.017	.676
83	1.44	17.896	.236	6.388

28

84	.491	.337	.101	.396
85	.051	.09	.087	.218
86	32.507	127.341	6.305	26.998
87	9.217	12.588	3.111	5.496
88	26.013	30.814	5.132	17.437

Functional Antagonism at α -1 Adrenoceptors

Functional assays indicative of pharmacologically defined α -1 adrenoceptors were used to further characterize compounds. Inhibition of phenylephrine (PE)-induced contraction of canine prostate smooth muscle can be correlated with α -1A adrenoceptor activation. Inhibition of PE-induced contraction of rat spleen is representative of α -1B adrenoceptor antagonism and inhibition of PE-induced contraction of rat vas deferens correlates with α -1A adrenoceptor antagonism (R. P. Burt, C. R. Chapple and I. Marshall, *Br. J. Pharmacol.* **107**: P324 (1992)). For each of these models, agonist dose response curves were repeated against increasing concentrations of test agent to derive a Schild plot [$\log (EC_{50} - 1)$ against \log (molarity of test agent)] to determine the pA_2 . Data for prazosin, terazosin and doxazosin actually demonstrate a more potent effect on spleen smooth muscle by approximately an order of magnitude.

Canine prostate strips were used *in vitro* as previously described (Hieble, J.P., Boyce, A.J. and Caine, M., *Fed. Proc.*, **45**: 2609-2614 (1986)), to determine antagonist potencies against phenylephrine-induced contractions.

The results are shown in Tables 2a and 2b. The results show that the compounds of the invention exhibit functional antagonism of α -1 adrenoceptors.

29

Table 2a.

In Vitro Data for Functional Antagonism at α -1 Adrenoceptors

Ex. No.	pA ₂ Rat Vas Deferens	pA ₂ Rat Spleen	pA ₂ Dog Prostate
	[α -1A]	[α -1B]	[α -1A]
1	8.49	8	9.29
2	8.4	8.16	9.16
3	8.33	7.91	8.68
5	8.19	8.36	9.16
8	8.52	8.26	9.34
9	8.62	8.05	9.39
10	8.04	6.89	8.97
11	8.69		8.92
12	8.07	8.17	7.67
13	8.12	8.37	9.07
33	8.95	7.69	8.87
39	8.53	7.52	
42	8.24	7.4	9.58
77	9.32	8.53	9.4
80	9.05	7.93	9.2
81	8.9	8.15	9.45
83	8.07	6.92	7.95
prazosin	8.78	9.51	7.59
terazosin	8.04	8.6	7.44
doxazosin	8.69	9.51	7.59

30

Table 2b.

In Vitro Data for Functional Antagonism at α -1 Adrenoceptors

Ex. No.	pA ₂ Dog Prostate [α -1A]	Ex. No.	pA ₂ Dog Prostate [α -1A]
4	7.91	53	8.71
6	7.32	54	9.05
7	7.62	55	8.31
14	9.01	56	8.78
15	8.27	57	8.14
16	7.91	58	8.9
17	8.94	59	8.48
18	8.38	60	9.15
19	8.3	61	8.64
20	8.83	62	8.59
21	7.88	63	8.87
22	8.82	64	8.81
23	8.32	65	8.63
24	8.89	66	8.94
25	9.17	67	8.33
26	9.23	68	8.28
27	8.63	69	9.24
28	8.32	70	8.95
29	8.91	71	8.45
30	8.94	72	8.57
31	8.63	73	8.91
32	7.47	74	8.77
34	8.98	75	9.18
35	7.06	76	8.73
36	8.27	77	9.4
37	9.62	78	8.03
38.	9.64	79	9.01
44	8.27	80	9.2
46	9.24	81	9.45
47	8.79	83	7.95

31

48	8.19	84	8.09
49	7.92	85	8.55
50	9.2	87	8.89
51	7.85	88	8.73

In Vivo Determination of Intraurethral Pressure (IUP) in Canines

The intraurethral pressure (IUP) model in aged canines is an accepted model of measuring the effect of prostate smooth muscle contraction on urethral tone.

- 5 Canines also have an enclosed prostate covering the urethral shaft thus providing an anatomical correlate with humans.

Beagle dogs (Marshall Farms) greater than 2 years of age and weighing between 12 and 15 kg were pre-anesthetized with thiopental sodium 15 mg/kg i.v. (Pentothal™, Abbott) and then placed under general anesthesia (isoflurane). A 7F
10 Swan-Ganz balloon catheter (Multiflex - list no. 41224-01, Abbott) was lubricated with a water soluble jelly, inserted into the urethral orifice and advanced approximately 40 cm in male dogs (considerably less in females) until the balloon tip was placed well inside the bladder. The balloon was then inflated with 1 mL of room air and the catheter slowly withdrawn just past the first resistance that is felt at
15 the bladder neck. Preliminary experiments in which dogs were sacrificed after such placement confirmed that this technique results in consistent positioning of the balloon within the prostatic urethra in males or the corresponding location in females. The balloon port of the catheter was connected to a Gould Statham P23Dd pressure transducer interfaced to a computerized data acquisition system (Modular
20 Instruments, Inc., Malvern, PA) for the measurement of intraurethral pressure (IUP).

Dogs were then treated with propranolol to block the β -adrenoceptor agonist effects of test agonists. Dose-response curves of the intraurethral pressor effect of epinephrine (EPI) were obtained before and after each of up to 3 increasing doses of
25 a test antagonist (i.v.). Fifteen minutes was allowed after each antagonist dose for equilibration before the next agonist dose-response was initiated. The increase in IUP caused by a given agonist dose was allowed to return to baseline before the next dose was given. The estimated antagonist dissociation constant (*in vivo* pseudo pA_2) was determined by Schild analysis (Brune, et al., Drug Development Research
30 (1995) in press).

32

The results are shown in Table 3. The results indicate that the compounds of the invention inhibit EPI induced increases in IUP.

Table 3

Inhibition of EPI Induced Increase in Canine IUP

Example	Canine IUP pseudo pA ₂
1	8.37
3	8.22
8	8.3
9	8.12
10	8.0
11	8.06
12	7.36
13	8.82
prazosin	7.88
terazosin	6.91
doxazosin	6.90

Spontaneously Hypertensive Rat (SHR) Model

The SHR model historically has been used as a predictor for the hypotensive effects of α -1 adrenoceptor antagonists. Male spontaneously hypertensive rats were anesthetized and the left femoral artery and vein catheterized for the measurement of mean arterial pressure (MAP) and drug administration respectively. The arterial catheter was connected to a Gould Statham p23ID transducer and the pressure waveform was recorded. MAP (mm Hg) and heart rate (HR, beats/min.) were determined on-line using a BUXCO Cardiovascular Analyzer. After a 30 minute pre-dose control period, each rat was given one dose of a test antagonist i.v. and the MAP and HR were monitored for an additional 2.5 hours. The area under the hypotensive response curve up to 60 minutes post dosing (T_{60} AUC) was determined using a trapezoidal rule integration of the percent change from control arterial pressure dataset.

The results are shown in Table 4. The results show that the compounds of the invention are weakly hypotensive.

Table 4
Spontaneously Hypertensive Rat (SHR) Assay

Example	SHR pseudo pA ₂
1	6.34
2	6.08
3	5.29
5	5.9
8	6.34
9	6
10	4.8
12	5.22
13	5.44
prazosin	7.4
terazosin	6.59
doxazosin	6.74

5

Pharmaceutical Compositions

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile

20

injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl
5 oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of
10 microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

15 In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form.
20 Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug
25 release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a
30 bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with
35 at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose,

35

glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, 5 e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage 10 form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be 15 prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances 20 and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active 25 compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, 30 tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

35

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

5 Compositions for rectal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum and release the active compound.

10 Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The
15 present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

20 Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*

25 Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

30 Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular patient, compositions, and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated, and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the
35 dosage until the desired effect is achieved.

Generally dosage levels of about 0.01 to about 50, more preferably of about 0.05 to about 5 mg of active compound per kilogram of body weight per day are administered orally to a mammalian patient. If desired, the effective daily dose may be divided into multiple doses for purposes of administration, e.g. two to four separate doses per day.

5 While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with a 5- α reductase inhibitor. A particularly preferred 5- α reductase inhibitor for use in coadministration with compounds of the present invention is the compound having the generic name finasteride.

10 Methods for preparing the compounds of the invention are shown in Schemes I-VI. In the following Schemes, R₁ and R₂ are independently hydrogen, alkoxy, hydroxy, alkyl, halo, carboxy, or alkoxycarbonyl.

Scheme I illustrates the general procedure for the preparation of the compounds of the invention. Compound 1, prepared by the procedures described in
15 United States patent No. 4,618,683, which is incorporated herein by reference, is reacted with chloroacetonitrile under mildly basic conditions (for example, diisopropylethylamine, triethylamine and the like) to afford the cyanomethyl compound 2. The nitrile is dissolved in an inert solvent (for example, THF, ether and the like) and treated with a reducing agent (for example, lithium aluminum
20 hydride, diborane or catalytic hydrogenation and the like) to give the ethylene diamine compound 3. The diamine is reacted with the isocyanate 4 of the aromatic compound U, prepared from the aromatic amine by treatment with phosgene or triphosgene, to give the pyrimidine dione 5.

Alternatively as shown in Scheme II, the diamine can be prepared by taking
25 diester 6, prepared by the procedures described in United States patent No. 5,049,564, which is incorporated herein by reference, in an inert solvent (for example, THF or ether and the like) and reducing the diester with a reducing agent (for example, lithium aluminum hydride or diborane and the like) to give the diol 7. The diol is reacted with an appropriate reagent to form leaving groups (for example,
30 a mesylate or tosylate and the like) giving compound 8. Treatment of compound 8 with the appropriate diamine (H₂N-(CH₂)_n-NH₂ or synthon) with heating gives the pyrrolidine amine 9. Compound 9 can be further elaborated by the procedures described in Scheme I to give the final compound 10.

The compounds of the invention can also be prepared by the procedures
35 illustrated in Scheme III. Compound 4a is reacted with a haloalkyl isocyanate (for example, 2-chloroethyl isocyanate) by the procedures described in *Eur. J. Med.*

Chem. 28: 499 (1993), which is incorporated herein by reference, to give haloalkyl urea 11. Compound 1, as previously described in Scheme I, is reacted with compound 11 to give the final product 5.

The preparation of chiral *cis* intermediates is shown in Scheme IV.

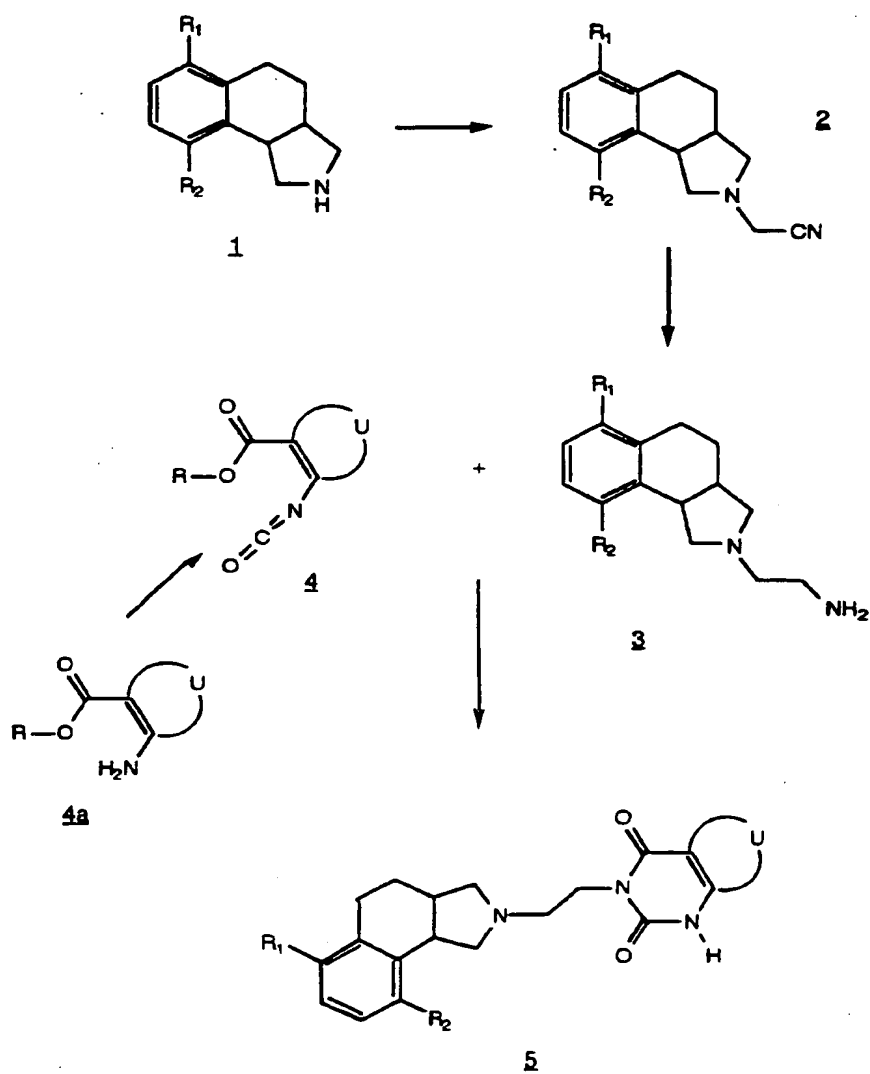
- 5 Dihydronaphthylene-1-carboxylic acid 12 is esterified (for example, using diazomethane or alcohol with a trace of sulfuric acid) to give compound 13. Treatment of the α,β -unsaturated ester with lithium cyanide in DMF and acetic acid affords the cyano compound 14. The nitrile ester is hydrolyzed (for example, using KOH in ethanol/water) to give the dicarboxylic acid 15. Treatment of the diacid with
10 acetic anhydride under reflux affords the cyclic anhydrides 16a and 16b. The anhydrides are reacted with optically active (S)-(-)- α -methylbenzylamine to give both the (3aR,9bR)-compound 18 and the (3aS,9bS)-compound 17 as a mixture of imides separable by crystallization. Compounds 17 and 18 are reduced (for example, with diborane) to give the corresponding N-substituted pyrrolidine
15 compounds 19 and 20. Catalytic hydrogenation affords chiral intermediates 21 and 22. These pyrrolidines can be further elaborated by the procedures described in Schemes I and III to give the final products.

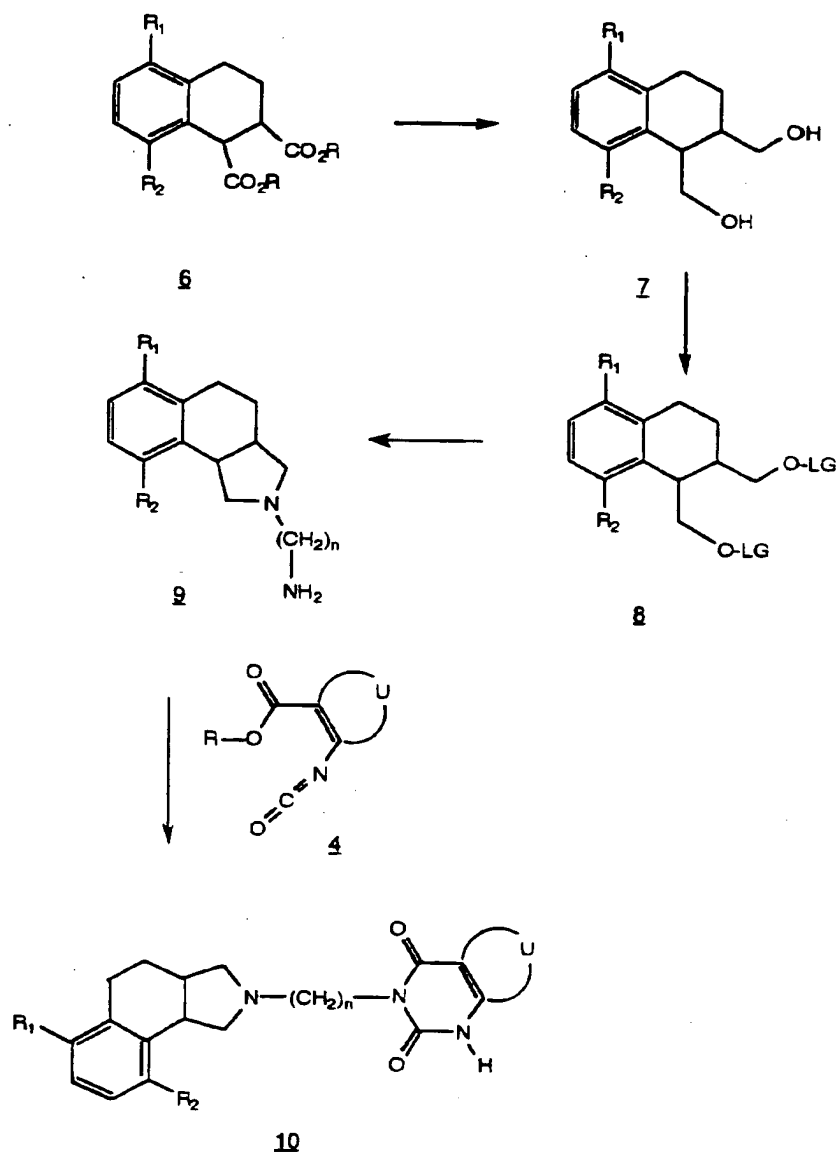
- A preferred embodiment is shown in Scheme V. Compound 23 wherein R is a carboxy protecting group is reacted with 2-chloroethyl isocyanate to give urea
20 24. Compound 24 is reacted with compound 25 in a solvent such as DMSO in the presence of a non-nucleophilic base such as diisopropylethylamine to give the ring closed coupled product 27.

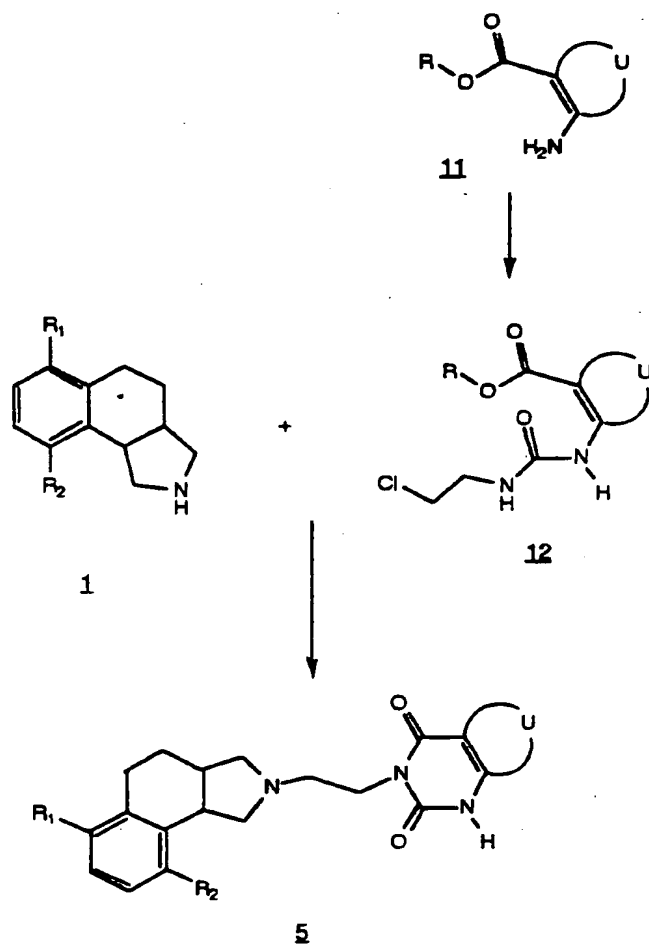
- Another preferred embodiment is shown in Scheme VI. The aromatic carboxy-protected amine 28 is reacted with triphosgene to give isocyanate 29. The
25 isocyanate is reacted with amine 30, prepared by the procedure described in Scheme I or II, to cyclize and couple in one step to give compound 31.

39

Scheme 1

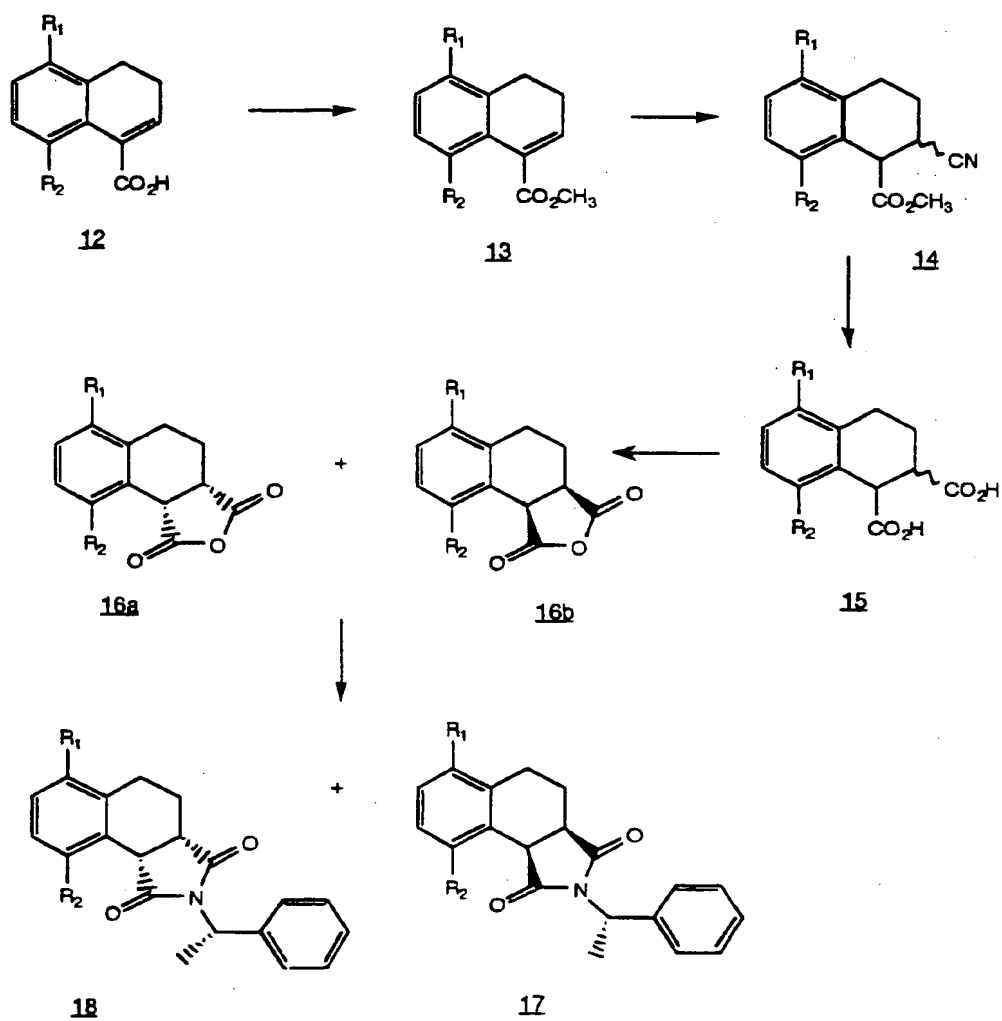


40
Scheme II

41
Scheme III

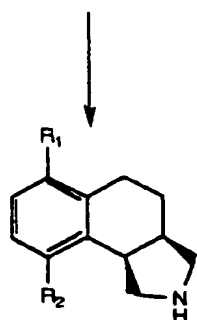
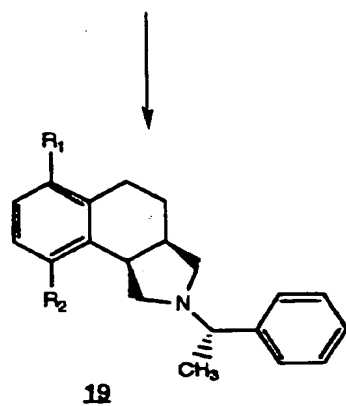
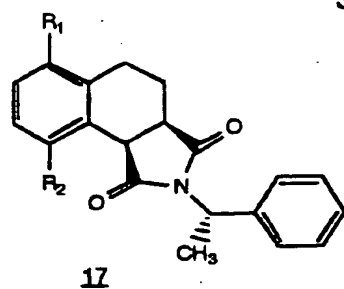
42

Scheme IV

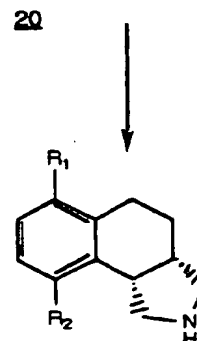
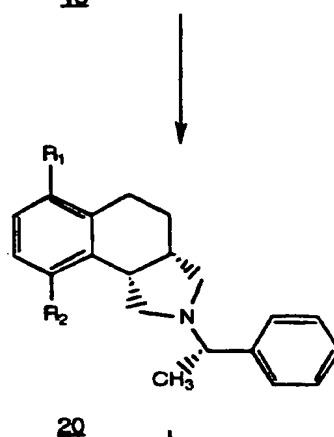
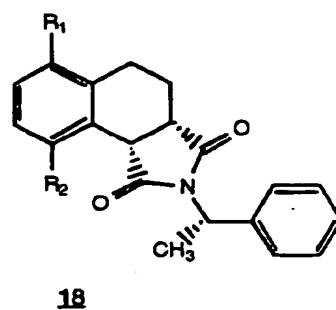


43

Scheme IV cont.



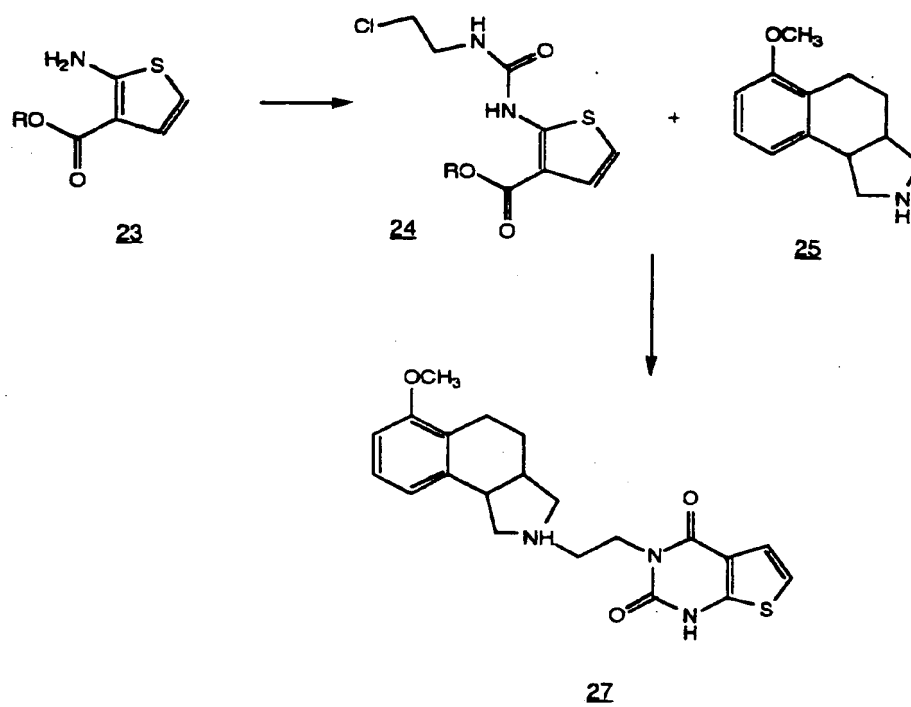
21



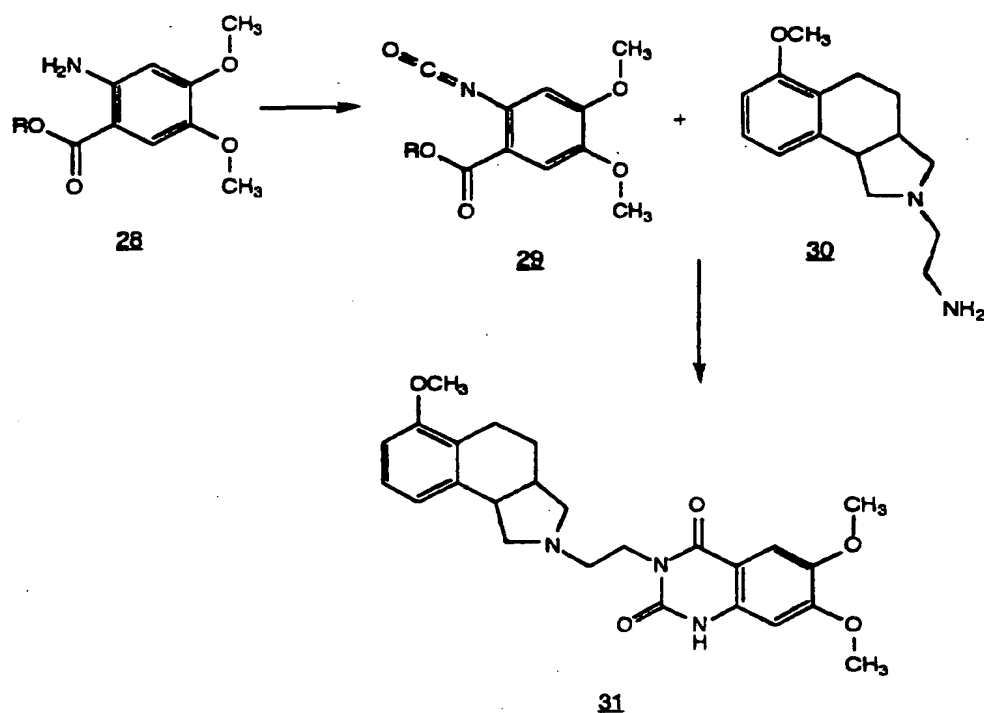
22

44

Scheme V



45
Scheme VI



The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

The following abbreviations were used: $\text{BH}_3\cdot\text{DMS}$ for borane dimethylsulfide complex, DMF for dimethylformamide, DMSO for dimethylsulfoxide, Et_3N for triethylamine, Et_2O for diethyl ether, EtOAc for ethyl acetate, EtOH for ethanol, KOtBu for potassium tert-butoxide, LDA for lithium diisopropylamide, MeOH for methanol, NaOEt for sodium ethoxide, iPrOH for isopropyl alcohol and THF for tetrahydrofuran.

46

Example 1

3-[2-(cis-9-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-[1H,3H]-quinazoline-2,4(1H,3H)-dione hydrochloride

5

Example 1A

cis-6-Methoxy-(2-cyanomethyl)-2,3,3a,4,5,9b-hexahydro-[1H]benz[e]isoindole

Cis-6-methoxy--2,3,3a,4,5,9b-hexahydro-[1H]benz[e]isoindole (2.39 g, 10 mmol), prepared by the procedures described in United States patent No. 4,618,683, which is incorporated herein by reference, and chloroacetonitrile (0.67 mL, 10.6 mmol) were combined in 10 mL acetonitrile and 5 mL ethyldiisopropylamine and heated at 70° C for 1 h. The reaction was quenched in 5% NaHCO₃, and extracted with ethyl acetate (2X). The organic extracts were washed with water (2X) and brine (1X), dried (Na₂SO₄) and evaporated to yield 2.20 g of the title compound as an off white solid (90%). ¹H NMR (300 MHz, CDCl₃) δ 1.60 (m, 2H), 1.80 (m, 1H), 2.58 (m, 3H), 2.77 (m, 1H), 3.23 (m, 2H), 3.48 (t, 1H), 3.64 (s, 2H), 3.81 (s, 3H), 6.70 (d, 1H), 6.74 (d, 1H), 7.12 (t, 1H).

Example 1B

cis-6-Methoxy-(2-(2-aminoethyl))-2,3,3a,4,5,9b-hexahydro-[1H]benz[e]isoindole

LiAlH₄ (2.40 g, 62 mmol) was suspended in THF (100 mL) and cooled to 0° C. The compound resulting from Example 1A (2.20 g, 9.0 mmol) was dissolved in THF (10 mL) and added dropwise to the above LiAlH₄ suspension. The reaction was then stirred at room temperature for 1.5 hours, quenched by addition of H₂O (2.2 mL), 15% NaOH (2.2 mL), and H₂O (6.6 mL), filtered through celite, washing with several portions of hot THF, and the solvent evaporated to yield the title compound (2.15 g, 93%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.50 (m, 3H), 1.72 (m, 1H), 2.19 (m, 2H), 2.52 (m, 3H), 2.70 (m, 1H), 2.80 (t, 1H), 3.21 (dd, 1H), 3.28 (t, 1H), 3.40 (m, 1H), 3.80 (s, 3H), 6.67 (d, 1H), 6.75 (d, 1H), 7.11 (t, 1H).

Example 1C**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-[1H,3H]-quinazoline-2,4(1H,3H)-dione hydrochloride**

2-Carboethoxy-phenylisocyanate (0.20 g, 1.0 mmol) was prepared by the
5 reaction of 2-carboethoxyaniline and triphosgene in toluene at reflux, followed by
removing the solvent *in vacuo*. The isocyanate and the compound resulting from
Example 1B (0.24 g, 1.0 mmol) were combined in 40 mL of toluene and heated at
reflux for 3 hours. The product was then partitioned between 5% NaHCO₃ and hot
ethyl acetate, and the organic phase was dried (K₂CO₃) and evaporated. The
10 resulting product was converted to its hydrochloride salt and recrystallized from
ethanol-ether to yield 0.12 g of the title compound as a white solid. ¹H NMR (300
MHz, DMSO-d₆) δ 7.92 (d, 1H), 7.65 (t, 1H), 7.12-7.27 (m, 2H), 7.08 (t, 1H),
6.72 (dd, 2H), 4.02 (t, 2H), 3.73 (s, 3H), 3.12-3.3 (m, 3H), 2.52-2.65 (m, 3H),
2.38-2.48 (m, 2H), 2.1-2.3 (m, 2H), 1.57-1.68 (m, 1H), 1.37-1.5 (m, 1H). Anal
15 calcd for C₂₃H₂₅N₃O₃ · HCl · H₂O: C, 61.95; H, 6.33; N, 9.42. Found: C,
61.94; H, 6.10; N, 9.18.

Example 2**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-methylthienol[3,2-d]pyrimidine-2,4(1H,3H)-dione hydrochloride**

20 2-Carbomethoxy-4-methyl-thiophene-3-isocyanate (0.22 g, 1.1 mmol),
prepared from the amine and triphosgene by the procedure described in Example 1C,
and the compound resulting from Example 1B (0.24 g, 1.0 mmol) were treated by
the procedures described in Example 1C to yield 0.12 g of the title compound as a
white solid. m.p. 255-257 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ
25 1.46-1.58 (m, 1H), 1.69-1.81 (m, 1H), 2.20-2.35 (m, 2H), 2.28 (d, 3H), 2.48-
2.60 (m, 2H), 2.64-2.90 (m, 3H), 3.36-3.50 (m, 3H), 3.81 (s, 3H), 4.21 (t, 2H),
6.67 (d, 1H), 6.74 (d, 1H), 7.10 (t, 1H), 7.31 (d, 1H). MS (DCI/NH₃) m/e 412
(M+H)⁺. Anal calcd for C₂₂H₂₅N₃O₃S · HCl · 0.5 H₂O: C, 57.82; H, 5.96; N,
9.19. Found: C, 58.01; H, 5.95; N, 9.08.

30

Example 3**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-thienol[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride**

2-Amino-3-carboethoxythiophene, prepared by the method of Gewald,
35 *Chem. Ber.* 98: 3571 (1965), was treated with 2-chloroethyl-isocyanate by the
procedures described by Romeo, *et al.* in *Eur. J. Med. Chem.*, **28**: 499-504 (1993).

48

The resulting urea (0.67 g, 2.4 mmol) and *cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindole (0.45 g, 2.2 mmol), prepared by the procedures described in United States patent No. 4,618,683, which is incorporated herein by reference, and 0.4 mL diisopropylethylamine in DMSO (1 mL) were heated at 100 °C for 1.5 hours. The reaction was quenched in H₂O and extracted with ethyl acetate. The combined organic extracts were dried and concentrated *in vacuo* resulting in a urea ester intermediate which was treated with 0.25 mL 1.0 M KOtBu in ethanol (2 mL) at reflux for 0.5 hours. After purification by column chromatography eluting with 95:5 ethyl acetate-ethanol and conversion to its HCl salt the title compound (0.30 g, 54%) was obtained as a white solid. m.p. 192-194 °C. ¹H NMR (500 MHz, DMSO-d₆) δ 1.53-1.63 (m, 1H), 1.75-1.82 (m, 1H), 2.38-2.55 (m, 1H), 2.60-2.68 (m, 1H), 2.68-2.78 (m, 1H), 2.91-3.05 (m, 1H), 3.33-3.54 (m, 3H), 3.71-3.86 (m, 1H), 3.78 (s, 3H), 3.93-4.24 (m, 4H), 6.75 (d, 1H), 6.83 (d, 1H), 7.11-7.20 (m, 3H). MS (DCI/NH₃) m/e 398 (M+H)⁺. Anal calcd for C₂₁H₂₃N₃O₃S · HCl · 0.25 H₂O: C, 57.53; H, 5.63; N, 9.58. Found: C, 57.48; H, 5.68; N, 9.43.

Example 4

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

2-Amino-3-carboethoxy-4-methylthiophene was treated with 2-chloroethyl-isocyanate by the procedures described in Example 3. The resulting urea (0.35 g, 1.2 mmol) and *cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro[1H]-benz[e]isoindole (0.23 g, 1.1 mmol) were treated by the procedures described in Example 3 to afford the title compound (0.11 g, 41%) was obtained as a white solid. m.p. 179-181 °C. ¹H NMR (500 MHz, DMSO-d₆) δ 1.40-1.48 (m, 1H), 1.60-1.67 (m, 1H), 2.12-2.19 (m, 1H), 2.24 (dd, 1H), 2.34 (s, 3H), 2.41-2.49 (m, 2H), 2.52-2.63 (m, 3H), 3.13 (t, 1H), 3.23-3.30 (m, 2H), 3.75 (s, 3H), 3.94 (t, 2H), 6.64 (s, 1H), 6.72 (d, 1H), 6.74 (d, 1H), 7.08 (t, 1H). MS (DCI/NH₃) m/e 412 (M+H)⁺. Anal calcd for C₂₂H₂₅N₃O₃S · HCl · 2 H₂O: C, 54.59; H, 6.25; N, 8.68. Found: C, 54.30; H, 5.64; N, 8.47.

Example 5

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

3-Amino-2-carboethoxythiophene was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.21 g, 1.15 mmol) and the compound resulting from Example 1B (0.24 g, 1.0

49

mmol) were treated by the procedures described in Example 1C to yield the title compound (0.12 g, 28%) as a white solid. m.p. 190-192 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.55-1.68 (m, 1H), 1.85-1.98 (m, 1H), 2.53-2.65 (m, 1H), 2.70-2.83 (m, 2H), 2.83-2.96 (m, 2H), 3.39-3.50 (m, 2H), 3.67 (q, 1H), 3.82 (s, 3H), 4.08-4.30 (m, 2H), 4.37 (t, 2H), 6.74 (t, 2H), 6.84 (d, 1H), 7.15 (t, 1H), 7.62 (d, 1H), 8.17 (bs, 1H). MS (DCI/NH₃) m/e 398 (M+H)⁺. Anal calcd for C₂₁H₂₃N₃O₃S · HCl · 0.75 H₂O: C, 56.37; H, 5.74; N, 9.39. Found: C, 56.32; H, 5.86; N, 8.90.

Example 6

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-5-phenyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride
2-Amino-3-Carboethoxy-4-phenylthiophene, prepared by the procedure of Gewald, et al, *Chem. Ber.* 94: 99 (1966), was treated with 2-chloroethylisocyanate by the procedures described by Romeo, et al. in *Eur. J. Med. Chem.*, 28: 499-504 (1993). The resulting urea (0.59 g, 1.65 mmol) and cis-6-methoxy-2,3,3a,4,5,9b-[1H]-benz[e]isoindole (0.31 g, 1.5 mmol) were treated by the procedures described in Example 3 to yield the title compound (0.15 g, 42%) as a white solid. m.p. 176-178 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 1.49-1.58 (m, 1H), 1.79-1.86 (m, 1H), 2.39-2.47 (m, 1H), 2.54-2.62 (m, 1H), 2.65-2.73 (m, 1H), 2.76-2.93 (m, 1H), 3.12-3.52 (m, 4H), 3.55-3.65 (m, 1H), 3.71-3.83 (m, 1H), 3.75 (s, 3H), 4.05-4.14 (m, 2H), 6.72 (d, 1H), 6.79 (d, 1H), 7.12 (t, 1H), 7.32-7.39 (m, 3H), 7.41 (dd, 2H). MS (DCI/NH₃) m/e 474 (M+H)⁺. Anal calcd for C₂₇H₂₇N₃O₃S · HCl · H₂O: C, 61.41; H, 5.73; N, 7.96. Found: C, 61.80; H, 5.83; N, 7.81.

Example 7

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-phenyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride
2-Amino-3-Carboethoxy-5-phenylthiophene, prepared by the procedure of Gewald, et al, *Chem. Ber.*, 94: 99 (1966), was treated with 2-chloroethylisocyanate by the procedures described in *Eur. J. Med. Chem.*, 28: 499-504 (1993). The resulting urea (0.42 g, 1.45 mmol) and cis-6-methoxy-2,3,3a,4,5,9b-[1H]-benz[e]isoindole (0.22 g, 1.1 mmol) were treated by the procedures described in Example 3 to yield the title compound (0.11 g, 42%) as a white solid. m.p. 248-250 °C (dec.). ¹H NMR (500 MHz, DMSO-d₆) δ 1.53-1.64 (m, 1H), 1.74-1.83 (m, 1H), 2.38-2.52 (m, 1H), 2.62-2.78 (m, 2H), 2.94-3.06 (m, 1H), 3.28-3.34 (m, 1H), 3.40-3.54 (m, 3H), 3.77 (s, 3H), 3.79-4.03 (m, 1H), 4.08-4.26 (m,

50

3H), 6.75 (bs, 1H), 6.83 (d, 1H), 7.16 (t, 1H), 7.32 (t, 1H), 7.42 (t, 2H), 7.61 (s, 1H), 7.67 (d, 2H). MS (DCI/NH₃) m/e 474 (M+H)⁺. Anal calcd for C₂₇H₂₇N₃O₃S · HCl · 0.5 H₂O: C, 62.48; H, 5.63; N, 8.10. Found: C, 62.39; H, 5.58; N, 8.04.

5

Example 8**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-thienof[3,4-d]pyrimidine-2,4(1H,3H)-dione hydrochloride**

3-Amino-4-carboethoxythiophene, prepared by the method of Baker, et al., *J. Org. Chem.*, 18: 138 (1953), was treated with 0.33 equivalent triphosgene. The resulting isocyanate (0.29 g, 1.6 mmol) and the compound resulting from Example 1B (0.30 g, 1.2 mmol) were treated by the procedure described in Example 1C to yield the title compound (0.15 g, 45%) as a white solid. m.p. 205-210 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.54-1.88 (m, 1H), 1.82-1.94 (m, 1H), 2.52-2.65 (m, 1H), 2.71-2.86 (m, 4H), 3.25-3.38 (m, 2H), 3.66-3.79 (m, 1H), 3.83 (s, 3H), 3.98-4.18 (m, 2H), 4.29 (t, 2H), 6.55 (d, 1H), 6.71 (d, 1H), 6.77 (d, 1H), 7.13 (t, 1H), 8.10 (d, 1H). MS (DCI/NH₃) m/e 398 (M+H)⁺. Anal calcd for C₂₁H₂₃N₃O₃S · HCl · 1.5 H₂O: C, 54.72; H, 5.90; N, 9.12. Found: C, 54.89; H, 5; N, 8.73.

15

Example 9**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-8-methoxy-quinazoline-2,4(1H,3H)-dione hydrochloride**

2-Methoxy-6-carboethoxyaniline was treated with 0.33 equivalent triphosgene. The resulting isocyanate (0.30 g, 1.1 mmol) and the compound resulting from Example 1B (0.25 g, 1.0 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.15 g, 33%) as a white solid. m.p. 233-235 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 7.68 (dd, 1H), 7.08-7.2 (m, 3H), 6.75 (t, 2H), 4.42 (m, 2H), 4.1-4.28 (m, 2H), 3.98 (s, 3H), 3.82 (s, 3H), 3.68 (q, 1H), 3.41 (m, 2H), 2.7-2.98 (m, 4H), 2.51-2.63 (m, 1H), 1.88-1.98 (m, 1H), 1.52-1.68 (m, 1H). MS (DCI/NH₃) m/e 422 (M+H)⁺. Anal calcd for C₂₄H₂₇N₃O₄ · HCl · 1.25 H₂O: C, 59.94; H, 5.83; N, 8.74. Found: C, 60.06; H, 5.74; N, 8.73.

25

30

Example 10**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione hydrochloride**

2-Carboethoxy-4,5-dimethoxyaniline was treated with 0.33 equivalent triphosgene. The resulting isocyanate (0.55 g, 2.2 mmol) and the compound

35

51

resulting from Example 1B (0.49 g, 2.0 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.60 g, 66%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ 7.3 (d, 1H), 7.18 (t, 1H), 6.7-6.9 (m, 3H), 4.1-4.3 (m, 3H), 3.9-4.1 (m, 1H), 3.85 (s, 3H), 3.8 (s, 3H), 3.7 (s, 3H), 3.4-3.58 (m, 4H), 2.92-3.6 (m, 2H), 2.6-2.85 (m, 2H), 1.73-1.88 (m, 1H), 1.52-1.68 (m, 1H). MS (DCI/NH₃) m/e 452 (M+H)⁺. Anal calcd for C₂₅H₂₉N₃O₅ · HCl: C, 61.53; H, 6.20; N, 8.61. Found: C, 61.29; H, 6.28; N, 8.45.

Example 11

10 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-7-chloro-quinazoline-2,4(1H,3H)-dione hydrochloride

2-Carboethoxy-5-chloroaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.26 g, 1.25 mmol) and the compound resulting from Example 1B (0.25 g, 1.0 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.12 g, 25%) as a white solid. m.p. >250 °C (dec.). ¹H NMR (300 MHz, DMSO-d₆) δ 7.95 (t, 1H), 7.28 (m, 2H), 7.18 (t, 1H), 6.84 (m, 1H), 6.75 (t, 1H), 3.95-4.3 (m, 4H), 3.78 (s, 3H), 3.42-3.58 (m, 4H), 2.92-3.1 (m, 2H), 2.6-2.85 (m, 2H), 1.7-1.86 (m, 1H), 1.52-1.68 (m, 1H). MS (DCI/NH₃) m/e 426 (M+H)⁺. Anal calcd for C₂₃H₂₄N₃O₃Cl · HCl · 0.25 H₂O: C, 59.17; H, 5.51; N, 9.00. Found: C, 59.10; H, 5.52; N, 8.95.

Example 12

25 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-5-methyl-quinazoline-2,4(1H,3H)-dione hydrochloride

2-Carbomethoxy-3-methylaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.28 g, 1.4 mmol) and the compound resulting from Example 1B (0.28 g, 1.1 mmol) were treated as described by the procedures described in Example 1C to yield the title compound (0.16 g, 28%) as a white solid. m.p. 178-180 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 7.38 (t, 1H), 7.17 (t, 1H), 6.92 (dd, 2H), 6.72 (dd, 2H), 4.12-4.42 (m, 4H), 3.82 (s, J=3, 3.68, q Hz, 1H), 3.4-3.58 (m, 2H), 2.93-3.06 (m, 2H), 2.7-2.85 (m, 2H), 2.73 (s, 3H), 2.51-2.65 (m, 1H), 1.87-2.0 (m, 1H), 1.53-1.7 (m, 1H). MS (DCI/NH₃) m/e 406 (M+H)⁺. Anal calcd for C₂₄H₂₇N₃O₃ · HCl · H₂O: C, 62.67; H, 6.57; N, 9.14. Found: C, 62.72; H, 6.17; N, 9.08.

52

Example 13

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

5

Example 13A5-Methoxy-3,4-dihydronaphthalene-1-carboxylic acid methyl ester

5-Methoxy-3,4-dihydronaphthalene-1-carboxylic acid (100 g, 490 mmol) was dissolved in 800 mL of methanol and 20 mL of 96% H₂SO₄, and heated at reflux for 18 hours. The reaction was then cooled and evaporated under reduced pressure to a volume of 100 mL, and quenched on ice. The aqueous mixture was extracted with diethyl ether (3 x 100 mL), and the organic phase was washed with water, 5% aqueous NaHCO₃, brine, and then dried (MgSO₄) and evaporated to yield 101 g (94%) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 2.36 (m, 2H), 2.78 (t, 3H), 3.83 (s, 6H), 6.82 (d, 1H), 7.14 (t, 1H), 7.19 (t, 1H), 7.40 (t, 1H).

15

Example 13B5-Methoxy-2-cyano-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid methyl ester

A solution of 1100 mL 0.5 M LiCN (550 mmol) in DMF and acetic acid (27.7 mL, 483 mmol) was prepared. The product resulting from Example 13A (101 g, 0.460 mmol) was dissolved in 100 mL DMF, and added over 15 minutes to the above solution. The reaction was stirred at 25 °C for 3.5 hours, and then poured onto ice/H₂O (5000 mL). The aqueous mixture was extracted with ether (3 x 500 mL), and the organic extracts were washed with H₂O and brine, dried (MgSO₄) and evaporated to dryness to yield 103.4 g (92%) of a light yellow oil as a mixture of *cis* and *trans* isomers of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 2.00 - 2.38 (m, 2H), 2.50 - 3.10 (m, 2H), 3.30 - 3.52 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.07 (m, 1H), 6.77 (d, 1H), 6.89 (d, 1H), 7.27 (m, 1H).

20

25

Example 13C5-Methoxy-1,2,3,4-tetrahydronaphthalene-1,2-dicarboxylic acid

30

The nitrile ester resulting from Example 13B (103 g, 422 mmol) was dissolved in 700 mL ethanol and 700 mL 45% aqueous KOH, and the reaction was heated at reflux for 10 hours. The cooled solution was diluted with 1.5 kg of ice and acidified to pH 1 with concentrated aqueous HCl. The resulting product was collected by filtration, washed with H₂O (3 x 200 mL) and dried under vacuum to yield 65.3 g (62%) of the title compound as a white solid. m.p. 200-201 °C. ¹H

35

53

NMR (300 MHz, CD₃OD) δ 1.85 (m, 1H), 2.27 (m, 1H), 2.65 (m, 1H), 2.85 (m, 1H), 3.10 (m, 1H), 3.80 (s, 3H), 4.05 (d, 1H), 6.79 (d, 1H), 6.92 (d, 1H), 7.11 (t, 1H).

Example 13D5 5-Methoxy-1,2,3,4-tetrahydronaphthalene-1,2-dicarboxylic anhydride

The compound resulting from Example 13C (65.3 g, 260 mmol) was dissolved in acetic anhydride (400 mL) and heated at reflux for 4 hours. The solvent was evaporated, and the resulting solid was triturated with 1:1 hexane:diethyl ether, and then collected and dried to yield 48.9 g (81%) of the title compound as a white solid. m.p. 138-140 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.97 (m, 1H), 2.28 (m, 1H), 2.47 (m, 1H), 2.95 (m, 1H), 3.55 (m, 1H), 3.83 (s, 3H), 4.32 (d, 1H), 6.83 (d, 1H), 7.17 (d, 1H), 7.27 (t, 1H).

Example 13E

15 (3aR,9bR)-6-Methoxy-((S)- α -methylbenzyl)-2,3,3a,4,5,9b-[1H]-
hexahydrobenz[elisoindole-1,3-dione and
(3aS,9bS)-6-Methoxy-((S)- α -methylbenzyl)-2,3,3a,4,5,9b-[1H]-
hexahydrobenz[elisoindole-1,3-dione

The compound resulting from Example 13D (48.8 g, 210 mmol) was combined with (S)-(-)- α -methylbenzyl amine (28.1 g, 0.230 mmol) in xylene (200 mL), and the reaction was heated to reflux with water removal (Dean Stark trap) until the theoretical amount of water was removed. The reaction was then cooled and diluted with ethyl acetate (300 mL). The resulting solution was washed with 5% aqueous HCl, 5% aqueous NaHCO₃ and brine, dried (MgSO₄) and evaporated to dryness. The resulting oily solid was triturated with diethyl ether, and the resulting crystalline title compound was collected (28.14 g, 81%) of the (3aR,9bR) product. m.p. 148 - 150 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.75 (d, 3H), 1.80 (m, 1H), 2.20 (m, 2H), 2.89 (m, 1H), 3.20 (m, 1H), 3.80 (s, 3H), 3.95 (d, 1H), 5.49 (q, 1H), 6.79 (d, 1H), 7.17 - 7.45 (m, 7H). From the mother liquor, on cooling, a second crop was collected (16.8 g, 48%) and shown to be the (3aS,9bS) product. m.p. 101-103 °C. ¹H NMR (300 MHz, CDCl₃) δ 1.78 (d, 3H), 1.85 (m, 1H), 2.20 (m, 2H), 2.88 (m, 1H), 3.17 (m, 1H), 3.81 (s, 3H), 3.98 (d, 1H), 5.48 (q, 1H), 6.78 (d, 1H), 7.17 - 7.42 (m, 7H).

54

Example 13F(3aR,9bR)-6-Methoxy-((S)- α -methylbenzyl)-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole hydrochloride

The (3aR,9bR) compound resulting from Example 13E (28.0 g, 83.5 mmol) was dissolved in THF (100 mL) and added over 5 minutes to a 1.0 M solution of BH₃ in THF. The reaction mixture was heated at reflux for 2 hours, and then cooled to 25 °C. Methanol (100 mL) was added cautiously, and after evolution of H₂ ceased, solvent was evaporated at reduced pressure. The resulting oil was dissolved in 2:1 methanol:isopropyl alcohol saturated with HCl (g), and the resulting solution was heated at reflux for 3 hours. The solvent was removed *in vacuo*, the resulting solid was triturated with 1:1 ethanol:diethyl ether, and the title compound (25.8 g, 90%) was collected by filtration. m.p. 229 - 231 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 1.38 (d, 3H), 1.49 (m, 1H), 1.57 (m, 1H), 2.07 (dd, 1H), 2.15 (m, 1H), 2.40 - 2.72 (m, 3H), 2.97 (dd, 1H), 3.21 (q, 1H), 3.49 (m, 2H), 3.81 (s, 3H), 6.68 (d, 1H), 6.77 (d, 1H), 7.11 (t, 1H), 7.19 - 7.38 (m, 5H).

Example 13G(3aR,9bR)-6-Methoxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole hydrochloride

The compound resulting from Example 13F (25.7 g, 74.7 mmol) was dissolved in methanol (700 mL) and 10% Pd/C (5.9 g) was added. The reaction was hydrogenated at 4 atmospheres of hydrogen at room temperature for 24 hours. The catalyst was removed by filtration, and the solvent was evaporated to yield 15.9 g (89%) of the title compound as a white solid. m.p. 223-225 °C. ¹H NMR (300 MHz, CD₃OD) δ 1.60 (m, 1H), 1.93 (m, 1H), 2.54 (m, 1H), 2.67 (m, 1H), 2.93 (m, 1H), 3.09 (dd, 1H), 3.13 (dd, 1H), 3.53 (m, 1H), 3.58 (dd, 1H), 3.67 (dd, 1H), 3.80 (s, 3H), 6.78 (d, 1H), 6.81 (d, 1H), 7.16 (t, 1H). [α]_D²⁰ = -22.0° (c=1.39, MeOH, free base).

Example 13H3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

2-Amino-3-carboethoxythiophene, prepared by the method of Gewald, *Chemische Berichte*, 98: 3571 (1965), was treated with 2-chloroethyl-isocyanate by the procedures described in *Eur. J. Med. Chem.* 28: 499 (1993). The resulting urea (1.65 g, 6.0 mmol) and the product from Example 13G (1.10 g, 5.4 mmol) were treated by the procedures described in Example 3 to yield 0.91 g (39%) of the title

55

compound as a white solid. m.p. 179-182 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ 1.52-1.66 (m, 1H), 1.80-1.92 (m, 1H), 2.49-2.65 (m, 3H), 2.69-2.83 (m, 2H), 3.18-3.38 (m, 2H), 3.59-3.70 (m, 1H), 3.82 (s, 3H), 3.96-4.10 (m, 2H), 4.30 (bt, 2H), 6.49 (d, 1H), 6.70 (d, 1H), 6.79 (d, 1H), 6.93 (d, 1H), 7.13 (t, 1H). MS (DCI/NH₃) m/e 398 (M+H)⁺. Anal calcd for C₂₁H₂₃N₃O₃S · HCl · 1.5 H₂O: C, 54.72; H, 5.90; N, 9.12. Found: C, 55.03; H, 6.03; N, 8.83.

Example 13I

(3aR,9bR)-2-Cyanomethyl-6-methoxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole

The compound resulting from Example 13G (2.39 g, 10.0 mmol) was dissolved in H₂O, basified to pH 12 with aqueous NaOH solution and extracted 3 x CH₂Cl₂. The organic extracts were dried (K₂CO₃), and evaporated to yield 1.96 g (9.64 mmol) of the free base. To the free base dissolved in CH₃CN (10 mL) and diisopropylethylamine (5 mL) was added 0.67 mL (10.6 mmol) of chloroacetonitrile. The reaction was heated at 70 °C for 1 hour, quenched in 5% NaHCO₃, and extracted with ethyl acetate (2x). The organic extracts were washed with water (2x) and brine (1x), dried (Na₂SO₄) and evaporated to yield 2.20 g of the title compound as an off white solid (90.5%). ¹H NMR (300 MHz, CDCl₃) δ 1.60 (m, 2H), 1.80 (m, 1H), 2.58 (m, 3H), 2.77 (m, 1H), 3.23 (m, 2H), 3.48 (q, 1H), 3.64 (s, 2H), 3.81 (s, 3H), 6.70 (d, 1H), 6.74 (d, 1H), 7.12 (t, 1H).

Example 13J

(3aR,9bR)-2-Aminoethyl-6-methoxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole

LiAlH₄ (0.82 g, 21.5 mmol) was suspended in THF (30 mL) and cooled to 0 °C. The compound resulting from Example 13I (0.80 g, 3.30 mmol) was dissolved in THF (5 mL) and added dropwise to the above LiAlH₄ suspension. The reaction was then stirred at room temperature for 1.5 hours, quenched by addition of H₂O (0.8 mL), 15% NaOH (0.8 mL) and H₂O (2.4 mL), filtered through celite, washing with several hot portions of THF, and the solvent evaporated to yield the title compound (0.75 g, 93%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.50 (m, 3H), 1.72 (m, 1H), 2.19 (m, 2H), 2.52 (m, 3H), 2.70 (m, 1H), 2.80 (t, 1H), 3.21 (dd, 1H), 3.28 (t, 1H), 3.40 (m, 1H), 3.80 (s, 3H), 6.67 (d, 1H), 6.75 (d, 1H), 7.11 (t, 1H).

56

Example 143-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-carbomethoxy-quinazoline-2,4(1H,3H)-dione hydrochloride

2,5-Bis-carbomethoxyaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.60 g, 2.4 mmol) and the compound resulting from Example 1B (0.48 g, 1.9 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.38 g, 37%) as a white solid. m.p. 230-233 °C (dec.). ¹H NMR (300 MHz, DMSO-d₆) δ 8.08 (d, 1H), 7.81 (s, 1H), 7.72 (d, 1H), 7.18 (t, 1H), 6.82 (d, 1H), 6.75 (d, 1H), 4.18-4.3 (m, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 3.4-3.6 (m, 4H), 2.85-3.1 (m, 2H), 2.55-2.85 (m, 4H), 1.7-1.83 (m, 1H), 1.52-1.65 (m, 1H). MS (DCI/NH₃) m/e 450 (M+H)⁺. Anal calcd for C₂₅H₂₇N₃O₅ · HCl · 0.5 H₂O: C, 60.66; H, 5.91; N, 8.49. Found: C, 60.91; H, 5.79; N, 8.39.

15

Example 153-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6-fluoro-quinazoline-2,4(1H,3H)-dione hydrochloride

2-Carboethoxy-4-fluoroaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.46 g, 2.2 mmol) and the compound resulting from Example 1B (0.46 g, 1.9 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.44 g, 55%) as a white solid. m.p. 208-210 °C (dec). ¹H NMR (300 MHz, DMSO-d₆) δ 7.55-7.7 (m, 2H), 7.28 (m, 1H), 7.17 (t, 1H), 6.71-6.88 (m, 2H), 3.95-4.33 (m, 3H), 3.87 (s, 3H), 3.68-3.75 (m, 1H), 3.4-3.58 (m, 4H), 2.92-3.08 (m, 1H), 2.58-2.85 (m, 2H), 2.32-2.48 (m, 1H), 1.7-1.87 (m, 1H), 1.5-1.7 (m, 1H). MS (DCI/NH₃) m/e 410 (M+H)⁺. Anal calcd for C₂₃H₂₄N₃O₃F · HCl · 0.5 H₂O: C, 60.72; H, 5.76; N, 9.24. Found: C, 60.35; H, 5.75; N, 9.04.

25

Example 163-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6-nitro-quinazoline-2,4(1H,3H)-dione hydrochloride

2-Carboethoxy-4-nitroaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.48 g, 2.1 mmol) and the compound resulting from Example 1B (0.46 g, 1.9 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.18 g, 25%) as a white solid. m.p. >250 °C (dec.). ¹H NMR (300 MHz, DMSO-d₆) δ

35

57

8.62 (d, 1H), 8.48 (dd, 1H), 7.32 (d, 1H), 7.08 (t, 1H), 6.72 (d, 2H), 4.03 (t, 2H), 3.73 (s, 3H), 3.18-3.25 (m, 4H), 2.4-2.7 (m, 4H), 2.22-2.32 (m, 2H), 1.37-1.53 (m, 1H), 1.6-1.7 (m, 1H). MS (DCI/NH₃) m/e 436 (M+H)⁺. Anal calcd for C₂₃H₂₄N₄O₅ · HCl · 0.25 H₂O: C, 57.86; H, 5.38; N, 11.73. Found: C, 57.87; H, 5.35; N, 11.50.

Example 17**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-6-methoxy-quinazoline-2,4(1H,3H)-dione hydrochloride**

2-Carboethoxy-4-methoxyaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.33 g, 1.5 mmol) and the product from Example 1B (0.32 g, 1.3 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.129 g, 25%) as a white solid. m.p. 159-161°; ¹H NMR (300 MHz, DMSO-d₆) δ 7.35 (m, 2H), 7.18 (m, 2H), 6.7-6.88 (m, 2H), 3.98-4.18 (m, 3H), 3.8 (s, 3H), 3.78 (s, 3H), 3.6-3.8 (m, 1H), 3.4-3.6 (m, 4H), 2.95-3.1 (m, 2H), 2.6-2.85 (m, 2H), 1.7-1.9 (m, 1H), 1.55-1.68 (m, 1H). MS (DCI/NH₃) m/e 422 (M+H)⁺. Anal calcd for C₂₄H₂₇N₃O₄ · HCl · H₂O: C, 60.56; H, 6.35; N, 8.83. Found: C, 60.54; H, 6.33; N, 8.55.

Example 18**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-6,7,8-trimethoxy-quinazoline-2,4(1H,3H)-dione hydrochloride**

2,3,4-Trimethoxy-6-carbomethoxyaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.50 g, 2.0 mmol) and the compound resulting from Example 1B (0.46 g, 1.9 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.22 g, 25%) as a white solid. m.p. 205-207 °C. ¹H NMR (300 MHz, DMSO-d₆) δ 7.12-7.25 (m, 2H), 6.71-6.88 (m, 2H), 3.95-4.3 (m, 4H), 3.88 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.42-3.57 (m, 4H), 2.93-3.08 (m, 1H), 2.62-2.83 (m, 2H), 2.34-2.48 (m, 1H), 1.72-1.87 (m, 1H), 1.52-1.68 (m, 1H). MS (DCI/NH₃) m/e 482 (M+H)⁺. Anal calcd for C₂₆H₃₁N₃O₆ · HCl · 0.25H₂O: C, 59.77; H, 6.27; N, 8.04. Found: C, 59.69; H, 6.30; N, 7.96.

58

Example 19**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-8-methyl-quinazoline-2,4(1H,3H)-dione hydrochloride**

2-Carboethoxy-6-methylaniline was treated with 0.33 equivalent triphosgene
5 by the procedures described in Example 1C. The resulting isocyanate (0.40 g, 2.0 mmol) and the compound resulting from Example 1B (0.46 g, 1.6 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.12 g, 18%) as a white solid. m.p. 250-252 °C (dec). ¹H NMR (300 MHz, DMSO-d₆) of the free base δ 7.8 (d, 1H), 7.5 (d, 1H), 7.05-7.13 (m, 2H), 6.72 (dd, 2H),
10 4.02 (t, 2H), 3.72 (t, 3H), 3.12-3.3 (m, 3H), 2.52-2.7 (m, 4H), 2.38-2.49 (m, 1H), 2.35 (s, 3H), 2.1-2.25 (m, 2H), 1.58-1.7 (m, 1H), 1.37-1.5 (m, 1H). MS (DCI/NH₃) m/e 406 (M+H)⁺. Anal calcd for C₂₄H₂₇N₃O₃ · HCl · 0.25 H₂O: C, 64.57; H, 6.43; N, 9.41. Found: C, 64.63; H, 6.36; N, 9.42.

15

Example 20**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,8-dimethyl-quinazoline-2,4(1H,3H)-dione hydrochloride**

2-Carboethoxy-4,6-dimethylaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate
20 (0.45 g, 2.1 mmol) and the compound resulting from Example 1B (0.46 g, 1.6 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.22 g, 30%) as a white solid. m.p. 273-4 °C (dec). ¹H NMR (300 MHz, DMSO-d₆) δ 7.62 (s, 1H), 7.39 (s, 1H), 7.18 (t, 1H), 6.7-6.9 (m, 2H), 4.2-4.3 (m, 2H), 4.08-4.2 (m, 1H), 3.8-4.1 (m, 1H), 3.8 (s, 1H), 3.4-3.58 (m, 4H),
25 2.88-3.1 (m, 2H), 2.6-2.83 (m, 2H), 2.33 (s, 3H), 2.3 (s, 3H), 1.72-1.85 (m, 1H), 1.48-1.68 (m, 1H). MS (DCI/NH₃) m/e 420 (M+H)⁺. Anal calcd for C₂₅H₂₉N₃O₃ · HCl: C, 65.85; H, 6.63; N, 9.22. Found: C, 65.60; H, 6.59; N, 9.03.

Example 21**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride**

2-Amino-3-ethoxycarbonylpyridine (0.46 g, 2.8 mmol), prepared from 2-aminonicotinic acid by the procedure described in *J. Chem. Soc.*, 1045 (1956) for 3-aminopicolinic acid, and Et₃N (0.74 mL, 5.3 mmol) were taken up in anhydrous
35 CH₂Cl₂ under N₂ and cooled to -78 °C. Phosgene (1.5 mL of 1.93 M solution in toluene, 2.8 mmol) was added, and the reaction was stirred at -78 °C for 45 minutes

59

and at 25 °C for 1.5 hours. The compound resulting from Example 1B in 4 mL of CH₂Cl₂ was added, and the reaction was stirred for 2 hours. The reaction mixture was partitioned between 1 M NaOH and CH₂Cl₂. The CH₂Cl₂ layer was dried (MgSO₄), filtered, concentrated *in vacuo* and taken up in THF (30 mL). To this solution was added 6 mL of 1 M potassium *tert*-butoxide in THF. The reaction was stirred for 1 hour at 25 °C and then was concentrated and chromatographed eluting with 5 % EtOH in CH₂Cl₂ saturated with NH₃ increasing the EtOH concentration to 10 %. The product (0.45 g, 40 %) was converted to its HCl salt which was recrystallized from EtOH/Et₂O. m.p. 234-236 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 1.47-1.61 (m, 1H), 1.72-1.86 (m, 1H), 2.27 (q, 2H), 2.49-2.61 (m, 1H), 2.64-2.77 (m, 2H), 2.84-2.95 (m, 1H), 3.05-3.16 (m, 1H), 3.53 (q, 1H), 3.76 (t, 2H), 3.80 (s, 3H), 4.17-4.35 (m, 2H), 6.67 (d, 1H), 6.77 (d, 1H), 6.90-6.96 (m, 1H), 7.09 (t, 1H), 8.05 (dt, 1H), 8.48 (dd, 1H). MS (DCI/NH₃) m/e 393 (M+H)⁺. Anal calcd for C₂₂H₂₄N₄O₃ · HCl · 0.75 H₂O: C, 59.73; H, 6.04; N, 12.66. Found: C, 59.57; H, 5.96; N, 12.39.

Example 22

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*c*]isoindol-1-yl)ethyl]-pyridol[3,2-*d*]pyrimidine-2,4(1H,3H)-dione hydrochloride

Following the procedure described for Example 21, 3-amino-2-ethoxycarbonylpyridine (0.30 g, 1.8 mmol), prepared by the method described in *J. Chem. Soc.*, 1045 (1956), Et₃N (0.48 mL, 3.4 mmol), phosgene (0.93 mL, 1.93 M in toluene, 1.8 mmol), and the compound resulting from Example 1B (0.40 g, 1.6 mmol) provided 0.51g (80%) of the desired product which was converted to its HCl salt. m.p. 195-198 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 1.47-1.62 (m, 1H), 1.74-1.87 (m, 1H), 2.47 (t, 2H), 2.50-2.76 (m, 3H), 2.97-3.07 (m, 1H), 3.13-3.25 (m, 1H), 3.46 (q, 1H), 3.70-3.83 (m, 2H), 3.78 (s, 3H), 4.24-4.43 (m, 2H), 6.65 (d, 1H), 6.77 (d, 1H), 7.07 (d, 1H), 7.12 (d, 1H), 7.31 (dd, 1H), 8.25 (d, 1H). MS (DCI/NH₃) m/e 393 (M+H)⁺. Anal calcd for C₂₂H₂₄N₄O₃ · HCl · 1.25 H₂O: C, 58.53; H, 6.14; N, 12.41. Found: C, 58.50; H, 5.83; N, 12.32.

Example 23

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*c*]isoindol-1-yl)ethyl]-5-chloro-quinazoline-2,4(1H,3H)-dione hydrochloride

2-Carboethoxy-3-chloroaniline was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.44 g, 2.1

60

mmol) and the compound resulting from Example 1B (0.40 g, 1.6 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.12 g, 18%) as a white solid. m.p. >250 °C (dec). ¹H NMR (300 MHz, CDCl₃) of the free base δ 7.35 (m, 2H), 7.18 (m, 2H), 7.0 (d, 2H), 6.73 (dd, 2H), 4.1-4.42 (m, 4H), 3.82 (s, 3H), 3.68 (q, 1H), 3.4-3.57 (m, 2H), 2.87-3.0 (m, 2H), 2.7-2.84 (m, 2H), 2.52-2.65 (m, 1H), 1.87-1.98 (m, 1H), 1.55-1.7 (m, 1H). MS (DCI/NH₃) m/e 426 (M+H)⁺. Anal calcd for C₂₃H₂₄N₃O₃Cl · HCl · 2 H₂O: C, 55.43; H, 5.86; N, 8.43. Found: C, 55.73; H, 5.60; N, 8.31.

Example 24

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-pyridol[3,4-d]pyrimidine-2,4(1H,3H)-dione dihydrochloride

Following the procedure described for Example 21, 3-amino-4-ethoxycarbonylpyridine (0.58 g, 3.5 mmol), prepared by substituting 3,4-pyridinedicarboximide for quinolinimide and the procedure described in *J. Chem. Soc.*, 1045 (1956), Et₃N (1.5 mL, 10.5 mmol), phosgene (1.8 mL of a 1.93 M solution in toluene, 3.5 mmol), and the compound resulting from Example 1B (0.60 g, 2.4 mmol) provided 0.68 g (71%) of the desired product which was converted to its HCl salt. m.p. 228-230 °C. ¹H NMR (300 MHz, CD₃OD) of the free base δ 1.45-1.49 (m, 1H), 1.66-1.78 (m, 1H), 2.22 (t, 1H), 2.33 (dt, 1H), 2.50-2.68 (m, 3H), 2.77-2.86 (m, 2H), 3.24-3.51 (m, 3H), 3.77 (s, 3H), 4.20 (t, 2H), 6.71 (dd, 2H), 7.07 (t, 1H), 7.91 (d, 1H), 8.39 (d, 1H), 8.55 (s, 1H). MS (DCI/NH₃) m/e 393 (M+H)⁺. Anal calcd for C₂₂H₂₄N₄O₃ · 2 HCl: C, 56.78; H, 5.63; N, 12.04. Found: C, 56.31; H, 5.63; N, 11.82.

Example 25

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-7-fluoro-quinazoline-2,4(1H,3H)-dione hydrochloride

2-Carboethoxy-5-fluoroaniline was treated with 0.33 equivalent triphosgene by the procedure described in Example 1C. The resulting isocyanate (0.46 g, 2.1 mmol) and the compound resulting from Example 1B (0.46 g, 1.9 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.49 g, 60%) as a white solid. m.p. 236-238 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 7.95 (q, 1H), 7.1 (t, 1H), 6.72-6.8 (m, 2H), 6.67 (d, 1H), 6.55 (dd, 1H), 4.15-4.35 (m, 2H), 3.81 (s, 3H), 3.43-3.75 (m, 2H), 2.78-3.15 (m, 2H), 2.5-2.8 (m, 3H), 2.3-2.47 (m, 2H), 1.48-1.87 (m, 3H). MS (DCI/NH₃) m/e 410

(M+H)⁺. Anal calcd for C₂₃H₂₄N₃O₃F · HCl · 0.25 H₂O: C, 61.00; H, 5.62; N, 9.29. Found: C, 61.33; H, 5.71; N, 9.33.

Example 26

5 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-quinazoline-2,4(1H,3H)-dione hydrochloride

N-Methyl-2-carboethoxyaniline (5.0 g, 28 mmol) was treated with 2-chloroethylisocyanate (2.86 mL, 28 mmol) at reflux in toluene for 18 hours. The reaction was cooled to 25 °C, and the crystalline product was collected by filtration
10 to yield the intermediate 1-methyl-3-(2-chloroethyl)-quinazoline-2,4-dione. The intermediate quinazolinedione (0.53 g, 2.2 mmol) and *cis*-6-methoxy-2,3,3a,4,5,9b-[1H]-benz[e]isoindole (0.38 g, 1.87 mmol) were combined in acetonitrile (3 mL) and diisopropylethylamine (0.8 mL) was added. The reaction mixture was heated at reflux for 18 hours. The resulting product was converted to
15 its HCl salt and recrystallized from acetone:ether to yield the title compound (0.30 g, 40%) as a white solid. m.p. 215-217 °C (dec). ¹H NMR (300 MHz, CDCl₃) of the free base δ 8.2 (dd, 1H), 7.7 (dt, 1H), 7.1-7.32 (m, 3H), 6.75 (t, 2H), 4.48 (m, 2H), 4.1-4.3 (m, 2H), 3.81 (s, 3H), 3.68 (m, 1H), 3.6 (s, 3H), 3.35-3.5 (m, 2H), 2.87-3 (m, 2H), 2.72-2.87 (m, 2H), 2.52-2.65 (m, 1H), 1.88-2.0 (m, 1H), 1.55-
20 1.7 (m, 1H). MS (DCI/NH₃) m/e 406 (M+H)⁺. Anal calcd for C₂₄H₂₇N₃O₃ · HCl · H₂O: C, 62.67; H, 6.57; N, 9.14. Found: C, 62.52; H, 6.51; N, 9.03.

Example 27

25 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-pyridol[4,3-d]pyrimidine-2,4(1H,3H)-dione dihydrochloride

Following the procedures described in Example 21, 4-amino-3-ethoxycarbonylpyridine (0.57 g, 3.4 mmol), prepared by the procedures described in *J. Org. Chem.*, 14: 97 (1949), Et₃N (0.85 mL, 6.1 mmol), phosgene (1.5 mL of a 1.93 M solution in toluene, 2.9 mmol), and the compound resulting from Example
30 1B (0.60 g, 2.4 mmol) provided 0.69 g (72 %) of the desired product which was converted to its HCl salt. m.p. 229-233 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 1.49-1.62 (m, 1H), 1.75-1.87 (m, 1H), 2.38 (t, 2H), 2.50-2.77 (m, 3H), 2.88-2.98 (m, 1H), 3.09-3.20 (m, 1H), 3.47 (q, 1H), 3.69 (bt, 2H), 3.80 (s, 3H), 4.15-4.37 (m, 2H), 6.63 (d, 1H), 6.67 (d, 1H), 6.78 (d, 1H), 7.10 (t, 1H),
35 8.47 (d, 1H), 8.98 (s, 1H). MS (DCI/NH₃) m/e 393 (M+H)⁺. Anal calcd for

62

$C_{22}H_{24}N_4O_3 \cdot 2 HCl \cdot 1.5 H_2O$: C, 53.66; H, 5.94; N, 11.38. Found: C, 53.83; H, 6.07; N, 11.31.

Example 28

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-1H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione hydrochloride

5 Ethyl-5-amino-1-methylpyrazole-4-carboxylate (0.40 g, 2.4 mmol) was dissolved in CH_2Cl_2 (10 mL) and triethylamine (0.68 mL, 4.89 mmol) and cooled to $-78^\circ C$. To the solution was added 1.93 M phosgene in toluene (1.23 mL, 2.4 mmol). After stirring at $-78^\circ C$ for 1 hour, and then $25^\circ C$ for 30 minutes, the
10 compound resulting from Example 1B (0.53 g, 2.2 mmol) was added. After 2 hours, the intermediate unsymmetrical urea was isolated. The intermediate product (0.70 g) in ethanol (10 mL) was treated with 1.0 M KOtBu in THF (2.0 mL) and the reaction was heated at $75^\circ C$ for 45 minutes. The reaction was quenched with 1.0 N HCl to yield the title compound as its HCl salt. Recrystallization from
15 methanol:ether yielded 0.420 g (45%) of a white solid. m.p. $>250^\circ C$ (dec). 1H NMR (300 MHz, CD_3OD) δ 1.67 (m, 1H), 1.92 (m, 1H), 2.60 (m, 1H), 2.83 (m, 3H), 3.30 (m, 3H), 3.52 (t, 2H), 3.68 (br s, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.32 (t, 2H), 6.79 (d, 1H), 6.82 (d, 1H), 7.18 (t, 1H), 7.85 (s, 1H). MS (DCI/ NH_3) m/e 396 ($M+H$)⁺. Anal calcd for $C_{21}H_{26}ClN_5O_3 \cdot 0.75 H_2O$: C, 56.63; H, 6.22; N, 15.72. Found: C, 56.77; H, 5.86; N, 15.84.

Example 29

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

25 2-Amino-3-carboethoxy-5-methylthiophene, prepared by the method of Gewald, et al., *Chem. Ber.*, 98: 94 (1966), was treated with 2-chloroethylisocyanate by the procedures described in *Eur. J. Med. Chem.*, 28: 499 (1993). The resulting urea (0.78 g, 2.7 mmol) and cis-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindole (0.49 g, 2.42 mmol) were treated by the
30 procedures described in Example 3 to yield 0.140 g (15%) of the title compound as a white solid. m.p. $>250^\circ C$ (dec). 1H NMR (300 MHz, $DMSO-d_6$) δ 1.60 (m, 1H), 1.80 (m, 1H), 2.40 (s, 3H), 2.50 (m, 1H), 2.70 (m, 2H), 3.00 (m, 2H), 3.42 (m, 3H), 3.79 (s, 3H), 4.11 (m, 1H), 4.18 (m, 3H), 6.76 (br d, 1H), 6.84 (d, 1H), 6.90 (s, 1H), 7.18 (t, 1H), 12.25 (br s, 1H). MS (DCI/ NH_3) m/e 412 ($M+H$)⁺.
35 Anal calcd for $C_{22}H_{26}ClN_3O_3S$: C, 58.98; H, 5.85; N, 9.38. Found: C, 58.58; H, 5.84; N, 9.08.

63

Example 30**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1H-pyrrolo[2,3-d]pyrimidine-2,4(3H,7H)-dione fumarate**

2-Amino-3,4-bis(ethoxycarbonyl)pyrrole, prepared by the method described in *J. Prakt. Chem.*, **314**: 303 (1972), was reacted with 2-chloroethylisocyanate by the procedures described in *Eur. J. Med. Chem.* **28**: 499 (1993). The resulting urea was reacted with *cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindole by the procedures described in Example 3. The urea ester intermediate (400 mg, 0.80 mmol) was treated with 5% KOH (50 mL) and heated at 110 °C for 1 hour. After cooling to room temperature the majority of the KOH was neutralized with concentrated HCl, followed by consumption of the remainder with solid NaHCO₃ resulting in the precipitation of the product at pH 12. The product was extracted into CH₂Cl₂, the organics dried (Na₂SO₄), filtered through celite and the solvent evaporated to give 196 mg of free base. The solid was dissolved in methanol and treated with a methanolic solution of fumaric acid (60 mg) to give 160 mg (39%) of the title compound as its fumarate salt. ¹H NMR (300 MHz, CD₃OD) δ 1.62 (m, 1H), 1.90 (m, 1H), 2.58 (ddd, 1H), 2.78 (m, 1H), 2.82 (dt, 1H), 3.18 (m, 2H), 3.40 (t, 2H), 3.62 (dd, 1H), 3.81 (s, 3H), 3.86 (dd, 1H), 4.01 (dd, 1H), 4.33 (t, 2H), 6.42 (d, 1H), 6.64 (d, 1H), 6.65 (s, 2H), 6.77 (d, 1H), 6.81 (d, 1H), 7.15 (t, 1H). MS (DCI/NH₃) m/e 381 (M+H)⁺. Anal calcd for C₂₅H₂₈N₄O₇ · 0.75 H₂O: C, 58.87; H, 5.83; N, 10.85. Found: C, 58.93; H, 5.73; N, 11.07.

Example 31**3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-phenylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione methanesulfonate**

2-Carboethoxy-3-amino-4-phenylthiophene, prepared by the method of Kirsch, *et al.*, *J. Heterocyclic Chem.*, **19**: 443 (1982), was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.90 g, 3.3 mmol) and the compound resulting from Example 1B (0.55 g, 2.2 mmol) were treated by the procedures described in Example 1C substituting methanesulfonic acid in the salt forming step, to yield the title compound (0.39 g, 38%) as a white solid. m.p. 268-271 °C. ¹H NMR (300 MHz, DMSO-d₆) δ 1.6 (m, 2H), 1.8 (m, 2H), 2.65 (m, 3H), 3.0 (m, 2H), 3.35-3.55 (m, 3H), 3.75 (s, 3H), 4.0-4.25 (m, 2H), 6.75 (m, 1H), 6.85 (m, 1H), 7.18 (t, 1H), 7.45 (m, 3H), 8.15 (m, 2H), 10.35 (s, 1H). MS (DCI/NH₃) m/e 474 (M+H)⁺. Anal calcd for

64

$C_{27}H_{31}N_3O_6S_2 \cdot 0.25 H_2O$: C, 58.57; H, 5.53; N, 7.32. Found: C, 58.62; H, 5.53; N, 6.99.

Example 32

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6-phenylthienof[3,2-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

5
2-Carboethoxy-3-amino-5-phenylthiophene, prepared by the method described in *Synthesis*, 275 (1984), was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting isocyanate (0.54 g, 2.1 mmol) and the compound resulting from Example 1B (0.40 g, 1.6 mmol) were
10 treated by the procedures described in Example 1C to yield the title compound (0.39 g, 38%) as a white solid. m.p. 229.5-231 °C. 1H NMR (300 MHz, DMSO- d_6) δ 1.6 (m, 2H), 1.8 (m, 2H), 2.65 (m, 3H), 3.0 (m, 2H), 3.35-3.55 (m, 3H), 3.75 (s, 3H), 4.0-4.25 (m, 2H), 6.8 (m, 2H), 7.18 (t, 1H), 7.3 (d, 1H), 7.5 (m, 3H), 7.8 (m, 2H), 10.35 (s, 1H). MS (DCI/ NH_3) m/e 474 (M+H) $^+$. Anal calcd for
15 $C_{27}H_{28}ClN_3O_3S \cdot 0.5 H_2O$: C, 62.48; H, 5.63; N, 8.10. Found: C, 62.29; H, 5.43; N, 8.10.

Example 33

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-4(3H)-one dihydrochloride

20 Ethyl 2-(N,N-dimethyl-N'-formamidinyl)-3,4-dimethoxybenzoate (1.68 g, 6.0 mmol), prepared from ethyl 6-amino-3,4-dimethoxybenzoate and using the procedures described by Gupton J.T., Miller J.F., Bryant R.D. Maloney P.R. and Foster B.S., *Tetrahedron*, 43(8): 1747 - 1752 (1987), and the compound resulting from Example 1C (0.59 g, 2.4 mmol) in 1,4-dioxane (20 mL) and p-toluenesulfonic
25 acid monohydrate (0.05 g, 0.2 mmol) were refluxed for 4 hours and then concentrated to a crude oil. Trituration with MeOH afforded the product as a free base (0.66 g, 63%). A portion (0.32 g) was dissolved in methylene chloride followed and treated with HCl(g) in Et $_2$ O to yield the title compound (0.37 g) as a
30 white solid. mp 180-185 °C (of a sample recrystallized from EtOH/Et $_2$ O). 1H NMR (300 MHz, D $_2$ O) δ 8.25 (s, 1H), 7.38 (br s, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.05 (s, 1H), 6.94 - 6.89 (d, 1H), 6.91 - 6.86 (s, 1H), 4.72 (s, 3H), 4.44 (t, J = 6.5 Hz, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 3.83 (s, 3H), 3.70 (br s, 3H), 3.24 - 3.10 (br s, 1H), 2.85 - 2.74 (m, 2H), 2.61 - 2.53 (m, 1H), 1.97 - 1.90 (m, 1H), 1.66 - 1.62 (m, 1H). MS (DCI/ NH_3) m/e 436 (M+H) $^+$. Anal calcd for
35 $C_{25}H_{29}N_3O_4 \cdot 0.7 HCl \cdot 0.4 EtOH$: C, 56.09; H, 6.22; N, 7.60. Found: C, 56.04; H, 6.35; N, 7.72.

Example 343-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-quinazoline-4(3H)-one dihydrochloride

5 Methyl 2-(N,N-dimethyl-N'-formamidinyl) benzoate was prepared according to the method of Gupton J.T., Miller J.F., Bryant R.D. Maloney P.R., and Foster B.S., *Tetrahedron*, **43**(8): 1747-1752 (1987). Methyl 2-(N,N-dimethyl-N'-formamidinyl) benzoate (1.7 g, 8.1 mmol) and the compound resulting from Example 1C (0.5 g, 2.0 mmol) were refluxed in a solution of 1,4-dioxane (25 mL) and p-toluenesulfonic acid monohydrate (0.04 g, 0.2 mmol) for 3 hours. The
10 reaction mixture was concentrated to a crude oil which was triturated with hexane to give a crude solid. The solid was collected by filtration and washed with EtOAc to give a white solid. The free base was dissolved in methylene chloride and treated with an ethereal solution of HCl to yield the title compound (0.40 g, 45%) as a white
15 solid. m.p. > 200 °C (on a sample recrystallized from EtOH/Et₂O). ¹H NMR (300 MHz, D₂O) δ 8.38 (s, 1H), 8.23 (br d, 1H), 7.94 (t, J = 7.6 Hz, 1H), 7.76 - 7.73 (d, 1H), 7.67 (t, J = 7.3 Hz, 1H), 7.26 (t, J = 7.9 Hz, 1H), 6.95 - 6.90 (d, 1H), 6.93 - 6.88 (d, 1H), 4.66 - 4.56 (m, 3H), 4.48 (t, J = 7.5 Hz, 2H), 3.84 (s, 3H), 3.72 - 3.60 (m, 3H), 3.18 (br s, 1H), 2.82 (br s, 2H), 2.62 - 2.53 (m, 1H), 1.97 -
20 1.90 (m, 1H), 1.65 (br s, 1H). MS (DCI/NH₃) m/e 876 (M+H)⁺. Anal calcd for C₂₃H₂₇Cl₂N₃O₂ · 0.3 HCl · 0.2 EtOH: C, 59.98 H, 6.13; N, 8.96. Found: C, 59.88; H, 6.17; N, 8.95.

Example 353-[2-(cis-6-Hydroxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrobromide

25 To a suspension of the compound resulting from Example 3 (100 mg, 0.23 mmol, 1.0 equiv) in 3 mL of methylene chloride cooled to -78 °C was added 0.46 mL of 1 M BBr₃ in methylene chloride (0.46 mmol, 2.0 equiv). The reaction was then warmed to room temperature and stirred for 5 hours. The oily suspension was
30 then cooled to -78 °C and quenched with 20 mL of dry methanol. The reaction solution was then evaporated to a tan solid which was crystallized from methanol-methylene chloride to furnish the title compound as a white powder (95 mg, 93%). m.p. > 200 °C. ¹H NMR (CD₃OD, 300 MHz) δ 1.60 (1H, m), 1.90 (1H, m), 2.57 (1H, m), 2.80 (2H, m), 3.30 (1H, m), 3.35 (1H, m), 3.55 (2H, t, J = 6.0 Hz),
35 3.62 (1H, m), 3.90 (2H, m), 4.35 (2H, t, J = 6.0 Hz), 4.95 (1H, m), 6.65 (2H, m), 7.0 (1H, t, J = 7.5 Hz), 7.06 (1H, d, J = 7.5 Hz), 7.25 (1H, d, J = 7.5 Hz).

66

MS (DCI/NH₃) m/e 384 (M+H)⁺. IR (KBr): 3400, 2720, 2650, 1720, 1640 cm⁻¹.
Anal calcd for C₂₀H₂₂N₃O₃SB: C, 51.73; H, 4.78; N, 9.05. Found: C, 51.39;
H, 4.76; N 8.78.

Example 36

5 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-quinazoline-2(1H)-one hydrochloride

Example 36A

10 2-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]aminomethyl-aniline

Using the procedure described by Langley D. R., Thurston, D. E, *J. Org. Chem.* 52 (1): 91-97 (1987), 2-nitrobenzyl bromide and the compound resulting from Example 13J were reacted with stannous chloride dihydrate in methanol to afford the title compound.

15 Example 36B

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-quinazoline-2(1H)-one hydrochloride

A solution of the compound resulting from Example 36A (136 mg, 0.387 mmol) in 4 mL of dry tetrahydrofuran was cooled and a solution of 75.3 mg (0.464 mmol) of N,N'-carbonyldiimidazole in 2 mL of dry tetrahydrofuran was added rapidly with stirring. The cooling bath was removed and stirring was continued for 3 hours. The solvent was evaporated to give the crude product. Chromatography on silica gel eluting with 3% MeOH in CHCl₃ afforded the product as a free base. The free base was dissolved in methylene chloride and treated with HCl(g) in Et₂O to yield the title compound (45 mg) as a white solid. m.p. 145-147 °C (on a sample recrystallized from EtOH/Et₂O). ¹H NMR (300 MHz, CD₃OD) δ 1.30 (m, 1H), 1.55-1.70 (m, 3H), 2.20 (m, 2H), 2.52-2.65 (m, 4H), 2.72 (m, 2H), 3.25 (m, 1H), 3.35 (s, 2H), 3.42 (m, 1H), 3.82 (s, 3H), 6.70 (m, 4H), 7.20 (m, 3H). MS (DCI/NH₃) m/c 378 (M+H)⁺. Anal. calcd for C₂₃H₂₈N₃O₂Cl · 0.9 HCl: C, 61.83; H, 6.52; N, 9.41. Found: C, 61.91; H, 6.46; N, 9.29.

Example 37

35 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione hydrochloride

Following the procedure described for Example 21, 6-amino-1,3-benzodioxole-5-carboxylic acid ethyl ester (0.51 g, 2.4 mmol), prepared in analogy

67

to the procedure described in J. Indian Chem. Soc., 64(6), 373-5 (1987), Et₃N (0.74 mL, 5.3 mmol), phosgene (1.3 mL 1.93 M solution in toluene, 2.4 mmol), and the compound resulting from Example 13J (0.50 g, 2.0 mmol) were reacted to give 0.82 g (93 %) of the desired product as its HCl salt. m.p. 257-258 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 1.46-1.61 (m, 1H), 1.71-1.86 (m, 1H), 2.22-2.36 (m, 2H), 2.50-2.75 (m, 3H), 2.80-2.92 (m, 1H), 3.03-3.13 (m, 1H), 3.40-3.52 (m, 1H), 3.63-3.76 (m, 2H), 3.81 (s, 3H), 4.15-4.35 (m, 2H), 6.00 (s, 2H), 6.23 (s, 1H), 6.65 (d, 1H), 6.76 (d, 1H), 7.08 (t, 1H), 7.23 (s, 1H). MS (DCI/NH₃) m/e 436 (M+H)⁺. Anal calcd for C₂₄H₂₅N₃O₅ · HCl: C, 61.08; H, 5.55; N, 8.90. Found: C, 60.81; H, 5.51; N, 8.78.

Example 38

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-ethylenedioxyquinazoline-2,4(1H,3H)-dione hydrochloride

Following the procedure described for Example 21, 7-amino-2,3-dihydro-1,4-benzodioxane-6-carboxylic acid ethyl ester (0.55 g, 2.4 mmol), prepared in analogy to the procedure described in United States patent No. 4,011,323 which is incorporated herein by reference, Et₃N (0.74 mL, 5.3 mmol), phosgene (1.3 mL 1.93 M solution in toluene, 2.4 mmol), and the compound resulting from Example 13J (0.50 g, 2.0 mmol) were reacted to give 0.91 g (99 %) of the desired product as its HCl salt. m.p. 212-214 °C. ¹H NMR (300 MHz, CDCl₃) of the free base δ 1.48-1.65 (m, 1H), 1.72-1.87 (m, 1H), 2.20-2.33 (m, 2H), 2.52-2.71 (m, 3H), 2.86-3.00 (m, 1H), 3.08-3.21 (m, 1H), 3.42-3.57 (m, 1H), 3.73-3.90 (m, 2H), 3.81 (s, 3H), 4.16-4.42 (m, 6H), 6.18 (s, 1H), 6.66 (d, 1H), 6.79 (d, 1H), 7.09 (t, 1H), 7.28 (s, 1H). MS (DCI/NH₃) m/e 450 (M+H)⁺. Anal calcd for C₂₅H₂₇N₃O₅ · HCl · 0.5 H₂O: C, 60.66; H, 5.91; N, 8.49. Found: C, 60.69; H, 5.73; N, 8.37.

Example 39

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

The compound resulting from Example 13J (2.44, 0.6 g) was reacted with 0.7g of the isocyanate derived from methyl 2-amino-4,5-dimethoxy-benzoate as in Example 10 to yield 0.6g (54%) of the title compound. ¹H NMR (300 MHz, DMSO-d₆) δ 7.36 (s, 1H), 7.18 (t, 1H), 6.81 (s, 1H), 6.85 (d, 1H), 6.75 (d, 1H), 4.2-4.32 (m, 3H), 3.9-4.1 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.8 (s, 3H), 3.65 (m, 1H), 3.42 (m, 3H), 2.92-3.6 (m, 2H), 2.6-2.85 (m, 2H), 1.73-1.88 (m, 1H),

68

1.52-1.68 (m, 1H). Anal calcd for $C_{25}H_{29}N_3O_5 \cdot HCl \cdot H_2O$: C, 59.34; H, 6.37; N, 8.30. Found: C, 59.73; H, 6.20; N, 8.23.

Example 40

5 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-1-methyl-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

The compound resulting from Example 13J (203 mg, 1 mmol) and 0.3 g (1.05 mmol) 6,7-dimethoxy-1-methyl-quinazoline-2,4-dione were reacted as described in Example 26 to yield 0.235 g (64%) of the title compound as a white
10 solid. m.p. 188-190 °C. 1H NMR (300 MHz, $CDCl_3$) of the free base δ 7.61 (s, 1H), 7.1 (t, 1H), 6.78 (d, 1H), 6.66 (d, 1H), 6.58 (s, 1H), 4.25 (t, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 3.81 (s, 3H), 3.6 (s, 3H), 3.42 (m, 3H), 2.48-2.87 (m, 5H), 2.28 (m, 2H), 1.75 (m, 1H), 1.52 (m, 1H). Anal calcd for $C_{25}H_{29}N_3O_5 \cdot HCl \cdot H_2O$: C, 60.05; H, 6.59; N, 8.08. Found: C, 59.51; H, 6.36; N, 7.93.

15

Example 41

3-[2-(cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6-methoxy-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

20

Example 41A

5-Amino-4-carboethoxy-2-methoxythiophene

To methanol (404 μ L, 10 mmol) in THF (10 mL) at 0 °C under nitrogen was added 2.5 M n-BuLi (4.0 mL, 10 mmol). After stirring 20 minutes, CS_2 (600 μ L, 10 mmol) was added and stirring was continued for 4 hours. The reaction was then
25 cooled to 0 °C followed by the addition of MeI (620 μ L, 10 mmol) whereupon the reaction was stirred for 4 hours at 0 °C then at ambient temperature overnight. In a separate flask the anion of acetonitrile was prepared by the dropwise addition of acetonitrile (520 μ L, 10 mmol) to a solution of LDA (10 mmol) in THF at -78 °C followed by stirring for 30 minutes at that temperature. To the acetonitrile anion was
30 added the solution of the xanthate prepared above. The reaction was stirred for 1 hour at -78 °C then 1 hour at 0 °C. The reaction was then cooled to -78 °C, treated with ethyl bromoacetate (1.1 mL, 10 mmol), warmed to reflux, treated with 1.0 M lithium bistrimethylsilylamide (1 mL) and heated at reflux for 1.5 hours. After cooling the reaction, it was partitioned between saturated $NaHCO_3$ solution and
35 methylene chloride. The organic layer was then dried with sodium sulfate, filtered,

69

concentrated *in vacuo* and flash chromatographed eluting with 4:1 hexane-ethyl acetate to give 343 mg (17% yield) of the title compound.

Example 41B

5 3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-1-yl)ethyl]-6-methoxy-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

The compound resulting from Example 41A (303 mg) was reacted according to the standard procedure for *in situ* isocyanate formation with the compound resulting from Example 13J (0.375 g, 1.52 mmol) to give 240 mg (38%) of product as the free base which was converted to the fumarate salt giving 149 mg (18%).
10 m.p. 217 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.45 (1H, m), 1.65 (1H, m), 2.23 (1H, m), 2.32 (1H, m), 2.44 (2H, m), 2.58 (1H, m), 2.66 (2H, m), 3.30 (3H, m), 3.75 (3H, s), 3.95 (2H, t), 3.99 (3H, s), 6.10 (1H, s), 6.59 (2H, s), 6.72 (1H, d), 6.75 (1H, d), 7.09 (1H, t), 11.76 (1H, br s). Anal calcd for C₂₆H₂₉N₃O₈S: C, 57.45; H, 5.38; N, 7.73. Found: C, 57.17; H, 5.23; N, 7.63.
15

Example 42

3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*e*]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-4(3H)-one dihydrochloride

20 Ethyl 2-(*N,N*-dimethyl-*N'*-formamidinyl)-3,4-dimethoxybenzoate (5.67 g, 20.3 mmol), prepared according to the method described by Gupton J.T., Miller J.F., Bryant R.D. Maloney P.R., Foster B.S. in Tetrahedron 43(8) 1747 - 1752 (1987) from ethyl 6-amino-3,4-dimethoxybenzoate, and The compound resulting from Example 13J (2.0 g, 8.1 mmol) refluxing in a solution of 1,4-dioxane (30 mL) and *p*-toluenesulfonic acid monohydrate (0.15 g, 0.8 mmol) for 4 hours. The
25 reaction mixture was concentrated to a crude oil which was recrystallized from MeOH to give the product as the free base. The free base was dissolved in methylene chloride and treated with HCl in Et₂O to yield the title compound (3.59 g, 87%) as a white solid. m.p. 180-185 °C (on a sample recrystallized from EtOH-Et₂O). ¹H NMR (300 MHz, D₂O) δ 8.31 (s, 1H), 7.42 (br s, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.08 (s, 1H), 6.94 - 6.89 (d, 1H), 6.91 - 6.87 (d, 1H), 4.72 (s, 3H), 4.45 (t, J = 6.5 Hz, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 3.83 (s, 3H), 3.70 (br s, 3H), 3.22 - 3.10 (br s, 1H), 2.85 - 2.74 (m, 2H), 2.62 - 2.51 (m, 1H), 1.97 - 1.90 (m, 1H), 1.66 - 1.62 (m, 1H). MS (DCI/NH₃) *m/e* 436 (M+H)⁺. [α]_D = +27.4°
30 (c=0.53, CH₃OH). Anal. calcd for C₂₅C₂₉N₃O₄ · 0.1 HCl · 0.8 H₂O: C, 57.03; H, 6.26; N, 7.98. Found: C, 57.10; H, 6.25; N, 7.93.
35

Example 433-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-4(3H)-one dihydrochloride

5 3-[(N,N-Dimethyl-N'-formamidinyl)]carboxyethylthiophene was prepared from 3-(2-amino)-carboxyethylthiophene by the method described in Gupton J.T., Miller J.F., Bryant R.D. Maloney P.R., Foster B.S., Tetrahedron 43(8) 1747 - 1752 (1987).

3-[(N,N-Dimethyl-N'-formamidinyl)]-carboxyethylthiophene (0.92 g, 4.1 mmol) and the compound resulting from Example 13J (0.40 g, 1.6 mmol) were heated under reflux in a solution of 1,4-dioxane (6.0 mL) and *p*-toluenesulfonic acid monohydrate (0.03 g, 0.2 mmol) for 3 hours. The reaction mixture was concentrated and then purified by flash column chromatography on silica gel eluting with EtOAc to give free base as an oil. The free base was dissolved in methylene chloride and treated with HCl(g) in Et₂O to yield the title compound (0.16 g, 22%) as a solid. m.p. 171-175 °C (on a sample recrystallized from MeOH-Et₂O). ¹H NMR (300 MHz, DMSO-d₆) δ 8.50 (br s, 1H), 7.64-7.62 (d, 1H), 7.44-7.42 (d, 1H), 7.16 (t, J = 9.5 Hz), 6.84-6.81 (d, 1H), 6.78-6.76 (d, 1H), 4.45-4.30 (br s, 2H), 4.13 (br s, 1H), 4.00 (br s, 1H), 3.77 (s, 3H), 3.70-3.45 (m, 3H), 3.01 (br s, 1H), 2.72 - 2.67 (m, 2H), 2.50 - 2.38 (m, 2H), 1.76 (br s, 1H), 1.60 (br s, 1H). MS (DCI/NH₃) m/e 882 (M+H)⁺. [α]_D = +19.1° (c=0.35, CH₃OH). Anal. calcd for C₂₁H₂₃N₃O₂S · 0.1 H₂O: C, 55.28; H, 6.56; N, 9.21. Found: C, 55.33; H, 5.72; N, 9.02.

Example 443-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-quinazoline-2(1H)-one hydrochloride

2-[(3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]aminomethyl aniline was prepared from 2-nitrobenzyl bromide and the compound resulting from Example 13J using stannous chloride dihydrate in methanol by the procedure of Langley D. R. and Thurston. D. E, *J. Org. Chem.* 52 (1), 91-97 (1987).

The above prepared compound (136 mg, 0.387 mmol) in 4 mL of dry tetrahydrofuran was cooled in an ice bath, and a solution of 75.3 mg (0.464 mmol) of N,N'-carbonyldiimidazole in 2 mL of dry tetrahydrofuran was added rapidly with stirring. The cooling bath was removed and stirring was continued for 3 hours. The solvent was evaporated to give the crude product. Chromatography on silica gel

71

eluting with 3% MeOH in CHCl_3 afforded the product as a free base. The free base was dissolved in methylene chloride and treated with a solution of HCl(g) dissolved in Et_2O to give the title compound (45 mg) as a white solid. m.p. 145-147 °C (on a sample recrystallized from $\text{EtOH-Et}_2\text{O}$). $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 1.30

5 (m, 1H), 1.55-1.70 (m, 3H), 2.20 (m, 2H), 2.52-2.65 (m, 4H), 2.72 (m, 2H), 3.25 (m, 1H), 3.35 (s, 2H), 3.42 (m, 1H), 3.82 (s, 3H), 6.70 (m, 4H), 7.20 (m, 3H). MS (DCI/ NH_3) m/e 378 ($\text{M}+\text{H}$)⁺. Anal. calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2 \cdot 0.90 \text{ HCl}$: C, 61.83; H, 6.52; N, 9.41. Found: C, 61.91; H, 6.46; N, 9.29.

Example 45

3-[2-(*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-1,2-dihydroquinazoline-4(3H)-one dihydrochloride

The compound resulting from Example 34 (0.15 g, 0.3 mmol) in methanol (25 mL) was hydrogenated at 4 atmosphere of H_2 at room temperature using a 10%
15 Pd/C catalyst (dry, 0.02 g) for 17 hours. The catalyst was removed by filtration and the filtrate concentrated. The residue obtained was dissolved in water, basified to pH 13 with potassium carbonate and extracted with Et_2O and EtOAc . The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give, after
20 flash column chromatography eluting with 10:90 EtOH-EtOAc , the free base as a white solid. The free base was dissolved in methylene chloride treated with a solution of HCl(g) dissolved in Et_2O to give the title compound (0.05 g, 37%) as a white solid. m.p. 130 °C (dec). $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 7.81 (dd, $J=1.5$ Hz, 1H), 7.79-7.78 (dd, $J=1.3$ Hz, 1H), 7.3-7.31 (m, 1H), 7.16 (t, $J=8.1$ Hz, 1H), 6.86-6.77 (m, 4H), 4.69 (s, 2H), 4.29-4.13 (m, 2H), 3.88-3.72 (m, 2H),
25 3.81 (s, 3H), 3.64-3.45 (m, 4H), 3.14-3.03 (m, 2H), 2.87-2.78 (m, 2H), 2.58-2.56 (m, 1H), 1.94-1.89 (m, 1H), 1.69-1.65 (m, 1H). MS (DCI/ NH_3) m/e 378 ($\text{M}+\text{H}$)⁺. Anal. calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2 \cdot 0.1 \text{ HCl} \cdot 0.8 \text{ H}_2\text{O}$: C, 58.97; H, 6.60; N, 8.97. Found: C, 59.06; H, 6.65; N, 8.59.

30

35

72

Example 46

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbamylquinazoline-2,4(1H,3H)-dione hydrochloride

5

Example 46A2-Amino-4-carbamylbenzoic acid

2-amino-4-Cyanobenzoic acid (3.01 g, 18.3 mmol), prepared by the method of Chan and Bruice, *J. Am. Chem. Soc.*, 99: 6721 (1977), was dissolved in 60 mL of 97% H₂SO₄ and heated to 45 °C for 12 h. The mixture was added to ice, and saturated Na₂CO₃ solution was added to adjust the pH = 3. The mixture was then filtered, and the yellow solid lyophilized to yield the title compound (2.94 g, 89%); mp 276-278 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.72 (br s, 3H), 7.90 (br s, 1H), 7.71 (d, 1H), 7.37 (br s, 1H), 7.21 (d, 1H), 6.92 (dd, 1H), 6.75 (br s, 2H); MS (DCI/NH₃) *m/z* 181 (M+H)⁺.

15

Example 46BMethyl 2-amino-4-carbamylbenzoate

The product from Example 46A (1.44 g, 8 mmol) was dissolved in 25 mL DMF and Me₂SO₄ (0.757 mL, 8 mmol) and Et₃N (1.23 mL, 8.8 mmol) were added. The reaction was stirred at room temperature for 24 hours, poured into brine, and extracted with 5x EtOAc. The extracts were washed with NaHCO₃ solution and brine, dried over MgSO₄, and the solvent evaporated. The residue was chromatographed on SiO₂ with EtOAc to yield the title compound (0.48 g, 31%); ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.91 (br s, 1H), 7.72 (d, 1H), 7.39 (br s, 1H), 7.24 (d, 1H), 6.93 (dd, 1H), 6.75 (br s, 2H), 3.80 (s, 3H); MS (DCI/NH₃) *m/z* 195 (M+H)⁺.

25

Example 46C

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbamylquinazoline-2,4(1H,3H)-dione hydrochloride

30

The product from Example 46B was treated with 0.33 equivalent triphosgene by the procedure described in Example 1C. The resulting isocyanate (0.40 g, 1.83 mmol) and the compound resulting from Example 13J (0.43 g, 1.74 mmol) were treated by the procedure described in Example 1C to yield the free base of the title compound which was chromatographed on SiO₂ using 18:1:1 EtOAc/HCOOH/water as eluent. The formic acid salt thus obtained was converted

35

73

to the HCl salt, yielding the title compound (0.12 g, 15%): mp >300 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.75 (d, 1H), 10.51 (s, 1H), 8.22 (s, 1H), 8.00 (t, 1H), 7.67 (m, 3H), 7.18 (t, 1H), 6.71-6.86 (m, 2H), 4.26 (m, 2H), 4.12 (m, 1H), 4.01 (m, 1H), 3.79 (s, 3H), 3.50 (m, 2H), 3.02 (m, 1H), 2.55-2.82 (m, 3H), 1.79 (m, 2H), 1.60 (m, 2H); MS (DCI/NH₃) *m/z* 435 (M+H)⁺. Anal. calcd for C₂₄H₂₇ClN₄O₄·HCl: C, 56.81; H, 5.56; N, 11.04. Found: C, 56.42; H, 5.32; N, 10.79.

Example 47

10 3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*eliso*indol-1-yl)ethyl]-7-(*N,N'*-dimethyl)carbonylquinazoline-2,4(1*H*,3*H*)-dione hydrochloride

Example 47A

Methyl 2-amino-4-(*N,N'*-dimethyl)carbonylbenzoate

15 Methyl 2-amino-4-carbonylbenzoate (0.94 g, 4.84 mmol) was added to a suspension of KOH (2.17 g, 38.7 mmol) in DMSO (15 mL). Iodomethane (1.05 mL, 16.9 mmol) was then added, and the reaction was stirred for 5 min, and poured into water (150 mL). The solution was extracted with 3x CH₂Cl₂, and the extracts were washed with 2x water, dried over MgSO₄, and evaporated. The residue was
20 chromatographed on SiO₂ using 4% MeOH/CH₂Cl₂ as eluent, to yield the title compound (0.66 g, 67%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.72 (d, 1H), 6.78 (br s, 2H), 6.74 (d, 1H), 6.48 (dd, 1H), 3.80 (s, 3H), 2.96 (br s, 3H), 2.87 (br s, 3H); MS (DCI/NH₃) *m/z* 223 (M+H)⁺.

25

Example 47B

3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[*eliso*indol-1-yl)ethyl]-7-(*N,N'*-dimethyl)carbonylquinazoline-2,4(1*H*,3*H*)-dione hydrochloride

Methyl 2-amino-4-(*N,N'*-dimethyl)carbonylbenzoate was treated with 0.33 equivalent triphosgene by the procedures described in Example 1C. The resulting
30 isocyanate (0.49 g, 1.95 mmol) and the compound resulting from Example 13J (0.44 g, 1.8 mmol) were treated by the procedures described in Example 1C to yield the free base of the title compound which was chromatographed on SiO₂ using 18:1:1 EtOAc/HCOOH/water as eluent. The formic acid salt thus obtained was converted to the HCl salt, yielding the title compound (0.13 g, 14%): mp >300 °C.
35 ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.81 (d, 1H), 11.25 (s, 1H), 7.96 (dd, 1H), 7.12-7.25 (m, 3H), 6.72-6.86 (m, 2H), 4.26 (m, 2H), 4.12 (m, 1H), 4.00 (m,

74

1H), 3.78 (s, 3H), 3.48 (m, 2H), 3.01 (s, 3H), 2.96 (m, 1H), 2.87 (s, 3H), 2.50-2.80 (m, 3H), 1.79 (m, 2H), 1.62 (m, 2H). MS (DCI/NH₃) *m/z* 463 (M+H)⁺.
Anal. calcd for C₂₆H₃₁ClN₄O₄•0.9HCl: C, 58.73; H, 6.10; N, 10.28. Found: C, 58.82; H, 6.17; N, 10.33.

5

Example 48

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,8-dichloro-7-methoxyquinazoline-2,4(1H,3H)-dione hydrochloride

10

Example 48AMethyl 2-Amino-3,5-Dichloro-4-methoxybenzoate

Chlorination of methyl 2-amino-4-methoxybenzoate according to the procedure of Hess, *et al.* (US Patent Number 4,287,341) gave the title compound: mp 72-73 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.86 (s, 3H), 3.92 (s, 3H), 6.33 (bs, 2H), 7.86 (s, 1H); MS (DCI/NH₃) *m/z* 250 (M+H)⁺.

15

Example 48B

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,8-dichloro-7-methoxyquinazoline-2,4(1H,3H)-dione hydrochloride

20

The product from Example 48A (498 mg, 2.0 mmol) was converted to the corresponding isocyanate by treatment with triphosgene as described in Example 1C. The resulting isocyanate (2.0 mmol) and the product from Example 13J (492 mg, 2.0 mmol) were refluxed in 30 mL of toluene for 16h and concentrated. The residue was triturated with EtOAc and filtered to give the free base which upon treatment with methanolic HCl gave the title compound as a tan solid (41 %): mp 229-233 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.54-1.68 (m, 1H), 1.70-1.85 (m, 1H), 2.43-2.53 (m, 1H), 2.55-2.82 (m, 3H), 2.93-3.10 (m, 1H), 3.40-3.55 (m, 3H), 3.77 (s, 3H), 3.91 (s, 3H), 3.97-4.15 (m, 2H), 4.19-4.28 (m, 2H), 6.73 (d, 1H), 6.83 (d, 1H), 7.17 (t, 1H), 7.98 (s, 1H), 10.86 (s, 1H), 11.32 (s, 1H). MS (DCI/NH₃) *m/z* 490 (M+H)⁺. Anal. calcd for C₂₄H₂₆Cl₃N₃O₄ • H₂O: C, 52.91; H, 5.18; N, 7.71. Found: C, 52.82; H, 4.81; N, 7.59.

25

30

35

75

Example 49

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-chloro-6-methoxyquinazoline-2,4(1H,3H)-dione hydrochloride

5

Example 49AMethyl 2-Amino-4-chloro-5-methoxybenzoate

A solution of 2-amino-4-chloro-5-methoxybenzoic acid (3.0 g, 15.0 mmol; prepared according to the procedure of Denny, *et al.*, *J. Med. Chem.* 34:217-222 (1991)) in 70 ml MeOH was treated with excess trimethylsilyl diazomethane. The solution was concentrated and the residue flash chromatographed on silica (9:1 hexane/EtOAc) to give the title compound (46%): mp 63-64 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.83 (s, 3H), 3.90 (s, 3H), 5.48 (bs, 2H), 6.75 (s, 1H), 7.39 (s, 1H); MS (DCI/NH₃) *m/z* 216 (M+H)⁺.

15

Example 49B

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-chloro-6-methoxyquinazoline-2,4(1H,3H)-dione hydrochloride

The product from Example 49A (387 mg, 1.8 mmol) was converted to the corresponding isocyanate by treatment with 0.33 eq of triphosgene as described in Example 1C. The resulting isocyanate (2.0 mmol) and the product from Example 13J (440 mg, 1.8 mmol) were refluxed in 30 mL of toluene for 16h and concentrated. The residue was triturated with EtOAc and filtered to give the free base which upon treatment with methanolic HCl gave the title compound (550 mg, 62%): mp 252-256 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.52-1.68 (m, 1H), 1.70-1.85 (m, 1H), 2.43-2.53 (m, 1H), 2.55-2.82 (m, 3H), 2.95-3.08 (m, 1H), 3.40-3.55 (m, 3H), 3.77 (s, 3H), 3.91 (s, 3H), 3.94-4.15 (m, 2H), 4.19-4.32 (m, 2H), 6.73-6.88 (m, 2H), 7.17 (t, 1H), 7.33 (s, 1H), 7.50 (s, 1H), 10.48 (s, 1H), 11.60 (s, 1H); MS (DCI/NH₃) *m/z* 456 (M+H)⁺. Anal. calcd for C₂₄H₂₇Cl₂N₃O₄• 0.3 H₂O: C, 57.91; H, 5.59; N, 8.44. Found: C, 57.89; H, 5.58; N, 8.31.

76

Example 50

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-1-methyl-7-methoxyquinazoline-2,4(1H,3H)-dione hydrochloride

5

Example 50AMethyl 2-formamido-4-methoxy benzoate

A mixture of acetic anhydride (7.15 g, 70 mmol) and formic acid was heated at 65 °C for 2h, cooled and added to a solution of methyl 2-amino-4-methoxybenzoate (2.5 g, 13.8 mmol) (US Patent 4,287,341) in 10 mL THF. The solution was stirred for 4h and concentrated to give the title compound in quantitative yield. ¹H NMR (300 MHz, CDCl₃) δ 3.88 (s, 3H), 3.91 (s, 3H), 6.64 (dd, *J* = 9.3 Hz, 1H), 7.97 (d, *J* = 9 Hz, 1H), 8.36 (d, *J* = 3 Hz, 1H), 8.52 (d, *J* = 2 Hz, 1H), 11.18 (bs, 1H); MS (DCI/NH₃) *m/z* 227 (M+NH₄)⁺.

15

Example 50BMethyl 2-aminomethyl-4-methoxy benzoate

The product from Example 50A (2.85 g, 13.6 mmol) in 25 mL THF at 0 °C was treated with BH₃ • SMe₂ (32 mmol). The solution was stirred for 2 h at 25 °C and carefully treated with methanol. The resulting solution was concentrated and the residue treated with TMEDA in THF. This solution was partitioned between EtOAc and 10 % aq sodium bicarbonate. The organic layer was washed with brine, dried MgSO₄, and concentrated. Flash chromatography on silica gel (9: 1 hexane/EtOAc) gave the title compound in 55% yield. ¹H NMR (300 MHz, CDCl₃) δ 2.89 (d, *J* = 5 Hz, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 6.09 (d, *J* = 3 Hz, 1H), 6.17 (dd, *J* = 9.3 Hz, 1H), 7.73 (bs, 1H), 7.83 (d, *J* = 9 Hz, 1H); MS (DCI/NH₃) *m/z* 196 (M+H)⁺.

25

Example 50C1-Methyl-7-methoxy benzoxazine-2,4(1H)-dione

To the product from Example 50B (390 mg, 2.0 mmol) and Et₃N (400 mg, 4.5 mmol) in 40 mL dichloromethane at -78 °C under nitrogen was added dropwise 1.93 M phosgene (4.0 mmol). The soln was stirred at 25 °C for 16 h and partitioned with brine. The methylene chloride layer was dried (MgSO₄) and concentrated to give the title compound as a white solid, quantitative yield: ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.48 (s, 3H), 3.93 (s, 3H), 6.85 (d, *J* = 3 Hz, 1H), 6.92 (dd, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 9 Hz, 1H); MS (DCI/NH₃) *m/z* 225 (M+NH₄)⁺.

35

77

Example 50D3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-1-methyl-7-methoxyquinazoline-2,4(1H,3H)-dione hydrochloride

The product from Example 50C (410 mg, 1.98 mmol) and the product from
5 Example 13J were refluxed in 30 mL of toluene for 16h, cooled and concentrated to
give the intermediate benzamide. To the crude benzamide (547mg, 1.34 mmol) and
triethylamine (400 mg, 4.5 mmol) in 20 mL toluene at -78 °C under nitrogen was
added dropwise 1.93 M phosgene (1.5 mmol). The solution was warmed to 25 °C
and then heated to reflux for 16h. The reaction mixture was concentrated and the
10 residue was flash chromatographed on silica gel (18:1:1 EtOAc / water / formic
acid). Treatment with methanolic HCl gave the desired product in 15 % yield: mp
248-249 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.52-1.68 (m, 1H), 1.70-1.85 (m,
1H), 2.33-2.53 (m, 1H), 2.55-2.85 (m, 2H), 2.95-3.08 (m, 1H), 3.40-3.60 (m,
4H), 3.52 (s, 3H), 3.77 (s, 3H), 3.91 (s, 3H), 3.94-4.15 (m, 2H), 4.19-4.35 (m,
15 2H), 6.71-6.93 (m, 4H), 7.17 (t, 1H), 7.98 (d, 1H), 10.74 (s, 1H); MS
(DCI/NH₃) *m/z* 436 (M+H)⁺. Anal. calcd for C₂₅H₃₀ClN₃O₄• H₂O: C, 61.38;
H, 6.58; N, 8.58. Found: C, 61.77; H, 6.41; N, 8.53.

Example 51

20 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-1-methyl-6-chloro-7-methoxyquinazoline-2,4(1H,3H)-dione hydrochloride

Example 51AMethyl 2-chloro-5-formamido-3-methoxybenzoate

25 The formamide was prepared in quantitative yield from methyl 2-amino-4-methoxy-5-chlorobenzoate (US Patent 4,287,341) as described in Example 50C.
¹H NMR (300 MHz, CDCl₃) δ 3.92 (s, 3H), 4.00 (s, 3H), 8.05 (s, 1H), 8.51 (s,
1H), 8.53 (d, *J* = 2 Hz, 1H), 11.17 (bs, 1H); MS (DCI/NH₃) *m/z* 261 (M+NH₄)⁺.

30

Example 51BMethyl 2-aminomethyl-5-chloro-4-methoxybenzoate

Borane reduction of the product from Example 51A as described previously
in Example 50B followed by flash chromatography (9:1 hexane/EtOAc) gave 700
mg (52%) of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 2.92 (d, *J* = 6
35 Hz, 3H), 3.82 (s, 3H), 3.94 (s, 3H), 6.09 (s, 1H), 7.81 (bs, 1H), 7.88 (s, 1H);
MS (DCI/NH₃) *m/z* 230 (M+H)⁺.

78

Example 51C1-Methyl-6-chloro-7-methoxy Benzoxazine-2,4(1H)-dione

The product from Example 51B was treated as described in Example 50C to give 500 mg (quantitative yield) of the title compound: ¹H NMR (300 MHz,

5 DMSO-*d*₆) δ 3.51 (s, 3H), 4.08 (s, 3H), 6.97 (s, 1H), 7.95 (s, 1H); MS (DCI/NH₃) *m/z* 259 (M+NH₄)⁺.

Example 51D*N*-[2-((3*aR*,9*bR*)-*cis*-6-Methoxy-2,3,3*a*,4,5,9*b*-hexahydro-[1*H*]-benz[*e*]isoindol-1-yl)ethyl]-2-aminomethyl-5-chloro-4-methoxy benzamide

10 The product from Example 51C (410 mg, 1.98 mmol) and the product from Example 13J were refluxed in 30 mL of toluene for 16 h, cooled and concentrated to give the intermediate benzamide which was flash chromatographed on silica gel (18:1:1 EtOAc / water / formic acid) to yield the title compound (760 mg, 86 %):

15 ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.40-1.50 (m, 1H), 1.60-1.72 (m, 1H), 2.12-2.29 (m, 2H), 2.40-2.52 (m, 1H), 2.52-2.66 (m, 3H), 2.81 (d, *J* = 6 Hz, 3H), 3.20 (m, 1H), 3.30 (m, 5H), 3.73 (s, 3H), 3.89 (s, 3H), 6.22 (s, 1H), 6.72 (d, *J* = 9 Hz, 1H), 6.73 (d, *J* = 9 Hz, 1H), 7.08 (dd, *J* = 9,9 Hz, 1H), 7.63 (s, 1H), 8.10-8.26 (m, 2H); MS (DCI/NH₃) *m/z* 444 (M+H)⁺.

Example 51E3-[2-((3*aR*,9*bR*)-*cis*-6-Methoxy-2,3,3*a*,4,5,9*b*-hexahydro-[1*H*]-benz[*e*]isoindol-1-yl)ethyl]-1-methyl-6-chloro-7-methoxyquinazoline-2,4(1*H*,3*H*)-dione hydrochloride

To the product from Example 51D (760 mg, 1.7 mmol) and triethylamine (500 mg, 5.0 mmol) in 20 mL toluene at -78 °C under nitrogen was added dropwise 1.93 M phosgene (2.0 mmol). The soln was warmed to 25 °C and stirred for 16 h. The reaction mixture was concentrated and the residue was flash chromatographed on silica gel (18:1:1 EtOAc / water / formic acid). Treatment with methanolic HCl gave the title compound (480 mg, 53%): mp 181-186 °C; ¹H NMR (300 MHz, 25 DMSO-*d*₆) δ 1.52-1.68 (m, 1H), 1.70-1.85 (m, 1H), 2.33-2.53 (m, 1H), 2.55-2.85 (m, 3H), 2.95-3.08 (m, 1H), 3.40-3.55 (m, 3H), 3.58 (s, 3H), 3.77 (s, 3H), 3.94-4.15 (m, 2H), 4.07 (s, 3H), 4.19-4.35 (m, 2H), 6.73 (d, 1H), 6.84 (d, 1H), 7.02 (s, 1H), 7.17 (t, 1H), 7.98 (s, 1H), 10.74 (s, 1H); MS (DCI/NH₃) *m/z* 470 (M+H)⁺. Anal. calcd for C₂₅H₂₉Cl₂N₃O₄• 1.25 H₂O: C, 56.77; H, 6.00; N, 30 7.94. Found: C, 56.74; H, 5.78; N, 7.67.

79

Example 52

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-(2-methoxyethyl)-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

5

Example 52AMethyl 2-[(2-methoxyethyl)amino]-4,5-dimethoxy benzoate

Methyl-2-amino-4,5-dimethoxybenzoate (2.1 g, 10 mmol), methoxyacetaldehyde (11 mmol), NaCNBH₃ (15 mmol) and acetic acid (10 mmol) were combined in 20 mL MeOH and stirred for 72 h. The reaction mixture was filtered through Celite, concentrated and the residue partitioned between water and EtOAc. The EtOAc layer was dried (MgSO₄) and concentrated to give the title compound (46%): ¹H NMR (300 MHz, CDCl₃) δ 3.40 (dt, J = 6.1 Hz, 2H), 3.43 (s, 3H), 3.65 (t, J = 6 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 3.91 (s, 3H), 6.21 (s, 1H), 7.38 (s, 1H), 7.80 (t, J = 1 Hz, 1H); MS (DCI/NH₃) m/z 270 (M+H)⁺.

15

Example 52B1-(2-methoxyethyl)-6,7-dimethoxy Benzoxazine-2,4(1H)-dione

The product from Example 52A was treated as described in Example 50C to yield the title compound (96%): ¹H NMR (300 MHz, CDCl₃) δ 3.35 (s, 3H), 3.76 (t, J = 6 Hz, 2H), 3.93 (s, 3H), 4.00 (s, 3H), 4.23 (t, J = 6 Hz, 2H), 6.93 (s, 1H), 7.45 (s, 1H); MS (DCI/NH₃) m/z 299 (M+NH₄)⁺.

20

Example 52C

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-(2-methoxyethyl)-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

25

The product from Example 52B (520 mg, 1.85 mmol) and the product from Example 13J were refluxed in 30 mL of toluene for 16h, cooled and concentrated to give the intermediate benzamide. To the crude benzamide (560mg, 1.16 mmol) and triethylamine (300 mg, 3.0 mmol) in 20 mL toluene at -78 °C under nitrogen was added dropwise 1.93 M phosgene (1.4 mmol). The solution was warmed to 25 °C and then heated to reflux for 16h. The reaction mixture was concentrated and the residue was flash chromatographed on silica gel (8:1:1 EtOAc / water / formic acid). Treatment with methanolic HCl gave the title compound (200 mg, 29%): mp 150-155 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 1.52-1.68 (m, 1H), 1.70-1.85 (m, 1H),

30

35

80

2.33-2.58 (m, 1H), 2.62-2.86 (m, 3H), 2.95-3.08 (m, 1H), 3.26 (s, 3H), 3.42-3.55 (m, 3H), 3.57-3.70 (m, 2H), 3.77 (s, 3H), 3.81 (s, 3H), 3.93 (s, 3H), 3.94-4.20 (m, 2H), 4.20-4.40 (m, 4H), 6.73 (d, 1H), 6.84 (d, 1H), 7.04 (s, 1H), 7.17 (t, 1H), 7.42 (s, 1H), 10.52 (s, 1H); MS (DCI/NH₃) *m/z* 510 (M+H)⁺. Anal.

5 calcd for C₂₈H₃₆ClN₃O₆ • 1.0 HCl • 1.0 H₂O: C, 56.00; H, 6.55; N, 7.00. Found: C, 56.02; H, 6.20; N, 6.94.

Example 53

10 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-5,6-methylenedioxyquinazoline-2,4(1H,3H)-dione hydrochloride

Example 53AMethyl 2-Amino-5,6-methylenedioxy benzoate

15 (Trimethylsilyl)diazomethane (6 mL of a 2M solution in hexane) was added to a solution of 5-*N*-(tert-butoxycarbonyl)amino-1,3-benzodioxole-4-carboxylic acid (1.56g, 9.1 mmol), prepared as described (*J. Org. Chem.*, 4549 (1989)). After stirring for 1 h, the reaction was concentrated and chromatographed (10:1 hexane:EtOAc). The resulting methyl ester was dissolved in CH₂Cl₂ and treated with TFA and stirred for 30 min. The reaction was concentrated and partitioned

20 between CH₂Cl₂ and NaHCO₃ solution. The organic layer was dried (MgSO₄), filtered, concentrated, and chromatographed on SiO₂ (5:1 hex:EtOAc) to yield the title compound (700 mg, 55 %): ¹H NMR (300 MHz, CDCl₃) δ 3.91 (s, 3H), 5.37 (bs, 2H), 5.97 (s, 2H), 6.12 (d, 1H), 6.80 (d, 1H); MS (DCI/NH₃) *m/z* 196 (M+H)⁺.

25

Example 53B

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-5,6-methylenedioxyquinazoline-2,4(1H,3H)-dione hydrochloride

Methyl 2-Amino-5,6-methylenedioxy benzoate (375 mg, 1.92 mmol) and triethylamine (0.70 mL, 5.0 mmol) were taken up in anhydrous CH₂Cl₂ under N₂ and cooled to -78°C. Phosgene (1.2 mL of 1.93 M soln in toluene) was added and the reaction was stirred at -78°C for 30 min and at 25 °C for 1.5 h. The product from Example 13J (in 10 mL CH₂Cl₂) was added and the reaction was stirred 18 h at 25 °C. The reaction was partitioned between CH₂Cl₂ and saturated aqueous

35 NaHCO₃. The organic layer was dried (MgSO₄), filtered, and concentrated. The residue was dissolved THF (100 mL) and KO^tBu (5 mL of 1 M soln in THF) was

81

added. After stirring for 1 h at 25°C the reaction was concentrated and partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The organic layer was dried (MgSO₄), filtered, concentrated and chromatographed on SiO₂ (1 % EtOH in CH₂Cl₂ saturated with NH₃) to provide the free base of the title compound (900 mg, 85 %) which was converted to the HCl salt: mp 204-208 °C; ¹H NMR (300 MHz, CDCl₃(free base)) δ 1.48-1.62 (m, 1H), 1.73-1.86 (m, 1H), 2.23-2.36 (m, 2H), 2.51-2.71 (m, 3H), 2.87-2.98 (m, 1H), 3.10-3.22 (m, 1H), 3.51 (q, 1H), 3.74-3.85 (m, 2H), 3.81 (s, 3H), 4.11-4.36 (m, 2H), 6.10 (s, 2H), 6.19 (d, 1H), 6.68 (d, 1H), 6.79 (d, 1H), 6.93 (d, 1H), 7.10 (t, 1H), 11.34 (bs, 1H); MS (DCI/NH₃) m/z 436 (M+H)⁺. Anal. calcd for C₂₄H₂₆ClN₃O₅: C, 61.08; H, 5.55; N, 8.90. Found: C, 60.33; H, 5.73; N, 8.61.

Example 54

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7,8-methylenedioxyquinazoline-2,4(1H,3H)-dione hydrochloride

Example 54A

Methyl 2-Amino-3,4-methylenedioxy benzoate

To a stirred mixture of 4-amino-1,3-benzodioxole (1.31g, 9.6 mmol), prepared as described in J. Chem. Soc., Perkin Trans. I, 259 (1991), hydroxylamine sulfate (8.2 g, 50 mmol), conc HCl (1 mL), and H₂O (10 mL) was added a slurry of chloral hydrate (1.8 g, 10.9 mmol), sodium sulfate (9.1g, 64 mmol), in H₂O (30 mL). After stirring at 60 °C for 1.5 h the reaction was kept at 25 °C over night. The brown solid was collected by filtration and washed with water. After drying under vacuum, the solid taken up in methanesulfonic acid (30 mL) and the solution was heated at 45 °C for 30 min. The reaction was cooled to 0° C and was poured onto 250 g of ice. A dark red solid was collected by filtration. The solid was taken up in a solution of NaOH (2 g solid) in water (14 mL). Hydrogen peroxide solution (30 %, 8 mL) was added over 30 min. The reaction was neutralized to pH 7 by the addition 1 M HCl. The 4-amino-1,3-benzodioxole-5-carboxylic acid was collected by filtration. (Trimethylsilyl)diazomethane (20 mL of a 2 M solution in hexane) was added to a solution of the acid in CH₂Cl₂ (25 mL) and methanol (2 mL). After stirring for 1 h, the reaction was concentrated and chromatographed on SiO₂ (hexane:EtOAc) to provide the title compound (475 mg, 25 %): ¹H NMR (300 MHz, CDCl₃) δ 3.85 (s, 3H), 5.51 (bs, 2H), 6.01 (s, 2H), 6.28 (d, 1H), 7.53 (d, 1H); MS (DCI/NH₃) m/z 196 (M+H)⁺.

Example 54B**3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7,8-methylenedioxyquinazoline-2,4(1H,3H)-dione hydrochloride**

Following the procedure described in Example 53B, the product from
5 Example 54A (475 mg, 2.44 mmol), Et₃N (0.74 mL, 5.3 mmol), phosgene (1.3
mL of 1.93 M solution in toluene), and the product from Example 13J (.50 g, 2.0
mmol) provided the free base of the title compound (0.77 g, 87 %) which was
converted to the HCl salt: mp 248-251 °C; ¹H NMR (300 MHz, CDCl₃(free base))
δ 1.45-1.58 (m, 1H), 1.72-1.83 (m, 1H), 2.17-2.27 (m, 2H), 2.47-2.76 (m, 3H),
10 2.80-2.90 (m, 1H), 3.03-3.14 (m, 1H), 3.42-3.54 (m, 1H), 3.68-3.82 (m, 2H),
3.80 (s, 3H), 4.15-4.35 (m, 2H), 6.08 (dd, 2H), 6.48 (d, 1H), 6.66 (d, 1H), 6.75
(d, 1H), 7.08 (t, 1H), 7.52 (d, 1H); MS (DCI/NH₃) m/z 436 (M+H)⁺; Anal. calcd
for C₂₄H₂₆ClN₃O₅: C, 61.08; H, 5.55; N, 8.90. Found: C, 60.80; H, 5.70; N,
8.68.

15

Example 55**3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione hydrochloride**

2-Hydroxy-4,5-methylenedioxy benzoic acid (0.67 g, 3.6 mmol), prepared
as described in *Synthesis* 763 (1988), was stirred at 70 °C with 2 mL of thionyl
chloride in 25 mL toluene for 30 min. After evaporation of the solvent, the residue
was azeotroped with toluene. The resulting acid chloride was taken up in CH₂Cl₂
(20 mL) and added slowly to a solution of the product from Example 13J (.75 g,
3.1 mmol) and Et₃N (0.64 mL, 4.6 mmol) in CH₂Cl₂. After stirring for 3 h at 25°C
the reaction was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃. The
25 layers are separated and aqueous layer was extracted with CH₂Cl₂. The combined
organics were dried (MgSO₄), filtered, concentrated, and chromatographed on SiO₂
(38:1:1 EtOAc:HCOOH:H₂O). 1.0g (66 %) of the intermediate amide as a free base
was obtained after a NaHCO₃/CH₂Cl₂ workup. The amide (850 mg, 2.1 mmol)
was taken up in CH₂Cl₂ (20 mL) and 1,1-carbonyldiimidazole (0.36 g, 2.2 mmol)
30 was added. After stirring for 2 h, the reaction was concentrated and
chromatographed (18:1:1 EtOAc:HCOOH:H₂O). After a NaHCO₃/CH₂Cl₂
workup, the free base of the title compound (650 mg, 72 %) was obtained and
converted to the HCl salt: mp 253-255 °C; ¹H NMR (300 MHz, CDCl₃(free base))
δ 1.45-1.58 (m, 1H), 1.68-1.79 (m, 1H), 2.20-2.31 (m, 2H), 2.46-2.59 (m, 2H),
35 2.63-2.86 (m, 3H), 3.29-3.44 (m, 3H), 3.81 (s, 3H), 4.15 (t, 2H), 6.11 (s, 2H),
6.67 (d, 1H), 6.69 (s, 1H), 6.75 (d, 1H), 7.10 (t, 1H), 7.36 (s, 1H); MS

83

(DCI/NH₃) *m/z* 437 (M+H)⁺; Anal. calcd for C₂₄H₂₅ClN₂O₆: C, 60.95; H, 5.33; N, 5.92. Found: C, 60.79; H, 5.14; N, 5.80.

Example 56

5 3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-4(3H)-one dihydrochloride

Ethyl 2-(*N,N'*-dimethyl-*N'*-formamidinyl)-4,5-dimethoxy benzoate was prepared from the known ethyl 2-amino-4,5-dimethoxy benzoate by the method of Gupton, J.T., Miller, J.F., Bryant, R.D., Maloney, P.R., Foster, B.S.

- 10 *Tetrahedron*, 1987, 43(8), 1747. Ethyl 2-(*N,N'*-dimethyl-*N'*-formamidinyl)-4,5-dimethoxy benzoate (2.5 g, 8.9 mmol) and the compound resulting from Example 13J (0.57 g, 2.3 mmol) were combined as in Example 43 to yield the title compound (0.67g, 57%) as a solid: mp 181-185 °C (EtOH/ CH₂Cl₂/Et₂O); [α]_D -22.3° (c 0.55 in MeOH); ¹H NMR (300 MHz, D₂O) δ 8.26 (s, 1H), 7.50 (s, 1H), 7.25 (t, *J*=7.9Hz, 1H), 7.14 (s, 1H), 6.95 - 6.93 (d, 1H), 6.90 - 6.87 (d, 1H), 4.81 - 4.70 (m, 3H), 4.45 (t, *J*=9.0Hz, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 3.84 (s, 3H), 3.72 - 3.68 (m, 3H), 2.90 - 2.75 (m, 3H), 2.63 - 2.54 (m, 1H), 1.97 - 1.85 (m, 1H), 1.67 - 1.60 (m, 1H); MS (DCI / NH₃) *m/z* 436 (M+H)⁺. Anal. calcd for C₂₅H₃₁Cl₂N₃O₄• 0.6 H₂O: C, 57.83 ;H, 6.25; N, 8.09. Found: C, 57.85; H, 6.25; N, 7.93.
- 20

Example 57

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7,8-dimethylquinazoline-4(3H)-one dihydrochloride

Methyl 2-(*N,N'*-dimethyl-*N'*-formamidinyl)-3,4-dimethyl benzoate was prepared from the known 2-amino-3,4-dimethyl benzoic acid (Rewcastle, G.W.; Atwell, G.J.; Zhuang, L.; Baguley, B.C.; Denny, W.A. *J. Med. Chem.*

- 25 1991, 34(1), 217) by the method of Gupton, J.T., Miller, J.F., Bryant, R.D., Maloney, P.R., Foster, B.S. *Tetrahedron* 1987, 43(8), 1747. Methyl 2-(*N,N'*-dimethyl-*N'*-formamidinyl)-3,4-dimethyl benzoate (0.5 g, 2.4 mmol) and the compound resulting from Example 13J (0.4 g, 2.0 mmol) were combined as in Example 43 to yield the title compound (0.53g, 56%) as a solid: mp 195-200 °C (EtOH/Et₂O); [α]_D +22.6° (c 0.46 in MeOH); ¹H NMR (300 MHz, MeOD) δ 8.89 (s, 1H), 8.11 - 8.08 (d, 1H), 7.54 - 7.51 (d, 1H), 7.17 (t, *J*=6.0 Hz, 1H), 6.84 - 6.79 (m, 2H), 4.53 (t, *J*=6.0Hz, 2H), 4.31 - 4.17 (m, 1H), 3.81 (s, 3H), 3.89 - 3.59 (m, 6H), 3.19 - 3.08 (m, 1H), 2.89 - 2.78 (m, 2H), 2.56 (s, 3H), 2.51 (s, 3H), 1.98 - 1.90 (m, 1H), 1.72 - 1.66 (m, 1H); MS (DCI / NH₃) *m/z* 404 (M+H)⁺.
- 35

84

Anal. calcd for $C_{25}H_{31}Cl_2N_3O_2 \cdot 0.3 H_2O \cdot 0.4 HCl$: C, 60.48; H, 6.49; N, 8.46.
 Found: C, 60.54; H, 6.52; N, 8.32.

Example 58

5 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-7,8-dimethoxyquinazoline-4(3H)-one dihydrochloride

Ethyl 2-(*N,N'*-dimethyl-*N'*-formamidinyl)-3,4-dimethoxy benzoate was prepared from the known ethyl 2-amino-3,4-dimethoxy benzoate (Hey, D.H.; Lobo, L.C. *J. Chem. Soc.* 1954, 2246) by the method of Gupton, J.T., Miller, J.F.,
 10 Bryant, R.D., Maloney, P.R., Foster, B.S. *Tetrahedron*, 1987, 43(8), 1747. Ethyl 2-(*N,N'*-dimethyl-*N'*-formamidinyl)-3,4-dimethoxy benzoate (0.76 g, 2.7 mmol) and the compound resulting from Example 13J (0.56 g, 2.3 mmol) were combined as in Example 43 to yield the title compound (0.13g, 11%) as a solid: mp 196-199 °C; $[\alpha]_D +27.2^\circ$ (c 0.37 in MeOH); 1H NMR (300 MHz, D_2O) δ 8.30 (s, 1H), 8.01 - 7.97 (d, 1H), 7.43 - 7.40 (d, 1H), 7.25 (t, $J=6.0$ Hz, 1H), 6.94 - 6.92 (d, 1H), 6.89 - 6.87 (d, 1H), 4.44 (t, $J=6.0$ Hz, 2H), 4.27 - 4.15 (m, 2H), 4.03 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H), 3.78 - 3.59 (m, 4H), 3.10 - 3.20 (m, 1H), 2.90 - 2.70 (m, 2H), 2.61 - 2.57 (m, 1H), 1.96 - 1.90 (m, 1H), 1.65 - 1.60 (m, 1H); MS (DCI/ NH_3) m/z 436 ($M+H$)⁺. Anal. calcd for $C_{25}H_{31}Cl_2N_3O_4 \cdot 0.6 H_2O$: C, 57.83; H, 6.25; N, 8.09. Found: C, 57.85; H, 6.33; N, 8.05.
 20

Example 59

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl]ethyl)-6-carbomethoxythienof[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

25 The free base of the compound resulting from Example 13H (240mg, 0.605 mmol) in THF (5mL) under N_2 at -78 °C was treated with LDA (2.1 equiv). The reaction was warmed to -5 °C for 45 min, then treated with methyl chloroformate (50 μ L, 1.05 equiv.) followed by stirring for 1 h. The reaction was evaporated to dryness and flash chromatographed to give the free base of the title compound (120 mg, 44%) which was converted to the HCl salt and recrystallized from EtOH/Et₂O
 30 to give the title compound (65 mg, 22%) as a light yellow solid: 1H NMR (300 MHz, CD_3OD) δ 1.65 (m, 1H), 1.92 (m, 1H), 2.60 (m, 1H), 2.83 (m, 2H), 3.3-3.4 (m, 3H), 3.55 (t, 2H), 3.66 (m, 1H), 3.81 (s, 3H), 3.90 (s, 3H), 4.10 (br m, 1H), 4.37 (t, 2H), 6.79 (d, 1H), 6.82 (d, 1H), 7.18 (t, 1H), 7.92 (s, 1H); MS (DCI/ NH_3) m/z 456; Anal. calcd for $C_{23}H_{26}ClN_3O_5S$: C, 56.15; H, 5.33; N, 8.54. Found: C, 55.99; H, 5.12; N, 8.33.
 35

Example 60

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-1H-benz[elisoindol-1-yl)ethyl]-6-carbomethoxythieno[3,2-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

- 5 The *R,R* enantiomer of the compound described in Example 5 (397mg, 1.00mmol), prepared from the product from Example 13J as described in Example 5, in THF (5 mL) at -5 °C under N₂ was treated slowly with LDA (2.1 equiv). After 60 min methyl chloroformate (80μL, 1 equiv.) was added and the reaction was stirred for an additional 1 h at 0 °C. The reaction was then quenched in saturated sodium bicarbonate and extracted with methylene chloride (3x). The organics were dried with sodium sulfate, filtered, solvent evaporated and flash chromatographed to give the free base of the title compound (110mg, 24%) which was converted to the HCl salt: ¹H NMR (300 MHz, CD₃OD) δ 1.65 (m, 1H), 1.94 (m, 1H), 2.60 (ddd, 1H), 2.82 (m, 2H), 3.3-3.4 (m, 3H), 3.58 (t, 2H), 3.67 (m, 1H), 3.81 (s, 3H), 10 3.95 (s, 3H), 4.10 (br m, 1H), 4.38 (t, 2H), 6.79 (d, 1H), 6.82 (d, 1H), 7.18 (t, 1H), 7.55 (s, 1H); MS (DCI/NH₃) *m/z* 456; Anal. calcd for C₂₃H₂₆ClN₃O₅S: C, 56.15; H, 5.33; N, 8.54. Found: C, 55.98; H, 5.16; N, 8.29.

Example 61

- 20 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-1H-benz[elisoindol-1-yl)ethyl]-5-carboethoxy-1H-pyrrolo[2,3-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

- The urea ester intermediate from Example 30 was dissolved in ethanol (10mL), treated with a 1.0 M solution of potassium *tert*-butoxide in THF (1.26 mL) and heated to 60 °C for 4 h then stirred overnight at room temperature. The reaction was concentrated, poured into saturated sodium bicarbonate and extracted with methylene chloride. The organic phases were combined, washed with water, then solvent evaporated to provide the free base of the title compound (220mg, 81%) as a white solid which was converted to HCl salt with 1.0 M HCl in Et₂O and 30 crystallized from ethyl acetate/ethanol: ¹H NMR (300 MHz, CD₃OD) δ 1.35 (t, 3H), 1.68 (m, 1H), 1.95 (m, 1H), 2.60 (ddd, 1H), 2.85 (m, 2H), 3.3-3.4 (m, 3H), 3.62 (t, 2H), 3.72 (m, 1H), 3.82 (s, 3H), 4.20 (br m, 1H), 4.27 (q, 2H), 4.34 (t, 2H), 6.79 (d, 1H), 6.81 (d, 1H), 7.18 (t, 1H), 7.32 (s, 1H); MS (DCI/NH₃) *m/e* 453. Anal. calcd for C₂₄H₂₉ClN₄O₅•0.5NaCl: C, 55.63; H, 35 5.64; N, 10.52. Found: C, 55.36; H, 5.68; N, 10.68.

86

Example 62

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-6-methoxy-7-phenylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione
hydrochloride

5 4-Amino-5-carboethoxy-2-methoxy-3-phenylthiophene (554mg, 2.0 mmol), prepared as described for 4-amino-5-carboethoxy-2-methoxythiophene in Example 41A, was converted in-situ to the corresponding isocyanate, reacted with the product from Example 13J and cyclized to provide the free base of the title compound (460 mg, 46%) which was converted to the HCl salt and crystallized to give the title
10 compound (220 mg, 20%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.45 (m, 1H), 1.63 (m, 1H), 2.08-2.24 (m, 2H), 2.44 (m, 1H), 2.55 (m, 3H), 3.15-3.30 (m, 4H), 3.75 (s, 3H), 3.96 (t, 2H), 3.99 (s, 3H), 6.72 (d, 1H), 6.73 (d, 1H), 7.08 (t, 2H), 7.3-7.5 (m, 5H), 11.22 (br s, 1H); MS (DCI/NH₃) *m/z* 504. Anal. calcd for C₂₈H₃₀ClN₃O₄S: C, 62.27; H, 5.60; N, 7.78. Found: C, 62.01; H, 5.48; N,
15 7.61.

Example 63

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-6-methoxy-7-ethylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione
hydrochloride

20 4-Amino-5-carboethoxy-3-ethyl-2-methoxythiophene (472mg, 2.06mmol), prepared as described for 4-amino-5-carboethoxy-2-methoxythiophene in Example 41A, was converted in-situ to the isocyanate, reacted with the product from Example 13J and cyclized to provide the free base of the title compound (240 mg, 26%) which was converted to the HCl salt and crystallized to give the title compound
25 (195mg, 19%): m.p. 208°; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.00 (t, 3H), 1.42 (m, 1H), 1.62 (m, 1H), 2.09-2.25 (m, 2H), 2.42 (m, 1H), 2.55 (m, 5H), 3.18 (t, 1H), 3.25 (m, 3H), 3.75 (s, 3H), 3.95 (t, 2H), 3.99 (s, 3H), 6.72 (d, 1H), 6.74 (d, 1H), 7.07 (t, 1H), 11.59 (br s, 1H); MS (DCI/NH₃) *m/z* 456. Anal. calcd for C₂₄H₃₀ClN₃O₄S: C, 58.59; H, 6.15; N, 8.54. Found: C, 58.40; H, 6.03; N,
30 8.41.

Example 64

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-6-methoxy-7-methylthieno[3,2-d]pyrimidine-2,4(1H,3H)-dione
hydrochloride

35 4-Amino-5-carboethoxy-2-methoxy-3-methylthiophene (415mg, 1.93mmol), prepared as described for 4-amino-5-carboethoxy-2-methoxythiophene

87

in Example 41A, was converted *in situ* to the isocyanate, reacted with the product from Example 13J and cyclized to give the free base of the title compound (420mg, 49%) which was treated with 1.0M HCl/Et₂O (1.5 mL) and crystallized to give the title compound (365mg, 40%) as the HCl salt: mp 205 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.45 (m, 1H), 1.63 (m, 1H), 1.99 (s, 3H), 2.20 (m, 2H), 2.45 (m, 1H), 2.55-2.65 (m, 3H), 3.20 (m, 1H), 3.27 (m, 3H), 3.75 (s, 3H), 3.96 (t, 2H), 3.99 (s, 3.0H), 6.72 (d, 1H), 6.74 (d, 1H), 7.08 (t, 1H), 11.60 (br s, 1H); MS (DCI/NH₃) *m/z* 442. Anal. calcd for C₂₃H₂₈ClN₃O₄S•0.25 H₂O: C, 57.25; H, 5.95; N, 8.71. Found: C, 57.23; H, 5.98; N, 8.59.

10

Example 65

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[clisoindol-1-yl)ethyl]-6-methoxy-7-isopropylthienol[3,2-d]pyrimidine-2,4(1H,3H)-dione
hydrochloride

15 4-Amino-5-carboethoxy-3-isopropyl-2-methoxythiophene (330mg, 1.36mmol), prepared in the same fashion as 4-amino-5-carboethoxy-2-methoxythiophene in Example 41A, was converted in-situ to the isocyanate, reacted with the product from Example 13J and cyclized to give 220 mg (34%) of the free base. This was treated with 1.0M HCl/Et₂O (1 mL) and crystallized to give the title
20 compound (100 mg, 15%): ¹H NMR (300 MHz, CDCl₃) δ 1.30 (d, 6H), 1.52 (m, 1H), 1.72 (m, 1H), 2.25 (m, 2H), 2.55 (m, 2H), 2.70 (m, 2H), 2.80 (m, 1H), 3.02 (sept, 1H), 3.40 (m, 3H), 3.80 (s, 3H), 4.00 (s, 3H), 4.06 (t, 2H), 6.67 (d, 1H), 6.75 (d, 1H), 7.09 (t, 1H), 9.32 (br s, 1H); MS (DCI/NH₃) *m/z* 470. Anal. calcd for C₂₅H₃₂ClN₃O₄S: C, 59.34; H, 6.37; N, 8.30. Found: C, 59.06; H,
25 6.39; N, 8.15.

88

Example 66

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7,8-dimethylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione dihydrochloride

5

Example 66A

5,6-dicarboximido-3,4-dimethyl-1-dimethylamino-1,4,5,6-tetrahydropyridine.

2-Methylbut-2-enal-dimethylhydrazone (1.67 g, 13.3 mmol) (A. Waldner *Helv Chim Acta* **1989**, 72, 1435) was reacted with maleimide (860 mg, 8.87 mmol) in acetonitrile (10 mL) at 60 °C for 4 h, cooled, the precipitate collected, washed
10 with diethyl ether and dried to provide the title compound (1.67 g, 85%).

Example 66B2,3-Dicarboximido-4,5-dimethylpyridine

The product from Example 66A (11.5 g, 51.8 mmol) was dissolved in
15 toluene (200 mL), treated with 70-230 mesh silica gel (23 g) and heated to 100 °C for 20 min. The reaction was cooled, filtered, washed with ethanol (250 mL) and solvents evaporated to give 8.34 g of a red solid. This material was heated to 50 °C in acetic acid (80 mL) while air was bubbled through the solution for 6h. The reaction was then cooled, the excess acetic acid evaporated, the residue treated with
20 aqueous sodium bicarbonate and extracted with methylene chloride (4x) and ethyl acetate (2x). The organics were dried with sodium sulfate, filtered, and solvent evaporated to give 6.45 g of crude product. This was dissolved in hot ethyl acetate and the title compound that separated upon cooling (1.5 g) was collected. The mother liquor was flash chromatographed to yield another 2.69 g of title compound
25 for a total of 4.19 g (51%).

Example 66CMethyl 4,5-dimethyl-3-aminopyridine-2-carboxylate

To the product from Example 66B (2.00 g, 11.4 mmol) in 10% NaOH (34 mL) was added slowly a solution of NaOBr prepared from bromine (650 µL, 1.1 equiv.) and ice cold 15% NaOH. The reaction was stirred 1h at room temperature then 1 h at 85 °C, cooled to 0 °C and carefully neutralized with concentrated HCl. At
30 pH 7 the carboxylic acid of the title compound precipitated, was collected, washed with water and dried to give 490 mg (26%). The acid was heated in methanol (5 mL) with sulfuric acid (2.3 mL) at 70 °C for 3 h, cooled, poured over ice,
35 neutralized with sodium bicarbonate and extracted with methylene chloride (4x).

The organics were dried with sodium sulfate, filtered, solvent evaporated and flash chromatographed to give the title compound (320 mg, 60%).

Example 66D

5 3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7,8-dimethylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione dihydrochloride

The product from Example 66C (380 mg, 2.11 mmol) was converted in-situ to the isocyanate as in Example 1C, reacted with the product from Example 13J and cyclized to give 675 mg (76%) of the free base of the title compound. This was
10 slurried in methanol, treated with 1.0M HCl/Et₂O (6 mL) and crystallized to give the title compound (520 mg, 49%): mp 223-226 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.52 (m, 1H), 1.73 (m, 1H), 2.27 (m, 2H), 2.35 (s, 3H), 2.40 (s, 3H), 2.55 (m, 2H), 2.68 (m, 1H), 2.81 (m, 2H), 3.40 (m, 3H), 3.80 (s, 3H), 4.28 (t, 2H), 6.65 (d, 1H), 6.74 (d, 1H), 7.09 (t, 1H), 8.40 (s, 1H); MS (DCI/NH₃) m/z 421. Anal.
15 calcd for C₂₄H₃₀Cl₂N₄O₃•0.75 H₂O: C, 56.86; H, 6.26; N, 11.05. Found: C, 56.85; H, 6.45; N, 11.08.

Example 67

3-[2-((3aR,9bR)-cis-9-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)butyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

20

Example 67A

(3aR,9bR)-9-Methoxy-((S)-α-methylbenzyl)-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole

cis-8-Methoxy-bis-(1,2-hydroxymethyl)-1,2,3,4-tetrahydronaphthalene-1,2-
25 bis mesylate (12.08 g, 31.9 mmol), prepared using the procedures described in United States patent No. 5,049,564, which is incorporated herein by reference, was dissolved in (S)-(-)-α-methylbenzylamine (60 mL), and the reaction was heated at 70 °C for 20 hours. Excess amine was removed *in vacuo*, and the product was partitioned between diethyl ether and 5% aqueous NaOH solution. The organic
30 phase was concentrated and purified by chromatography on silica gel eluting with 20% diethyl ether in hexanes to yield the title compound (3.4 g, 69%) as the first eluting product. ¹H NMR (300 MHz, CDCl₃) δ 1.37 (d, 3H), 1.61 (m, 2H), 1.93 (m, 1H), 2.12 (dd, 1H), 2.48 (m, 1H), 2.61 (m, 2H), 2.87 (dd, 1H), 3.18 (dd, 1H), 3.66 (m, 2H), 3.80 (s, 3H), 6.69 (d, 1H), 6.73 (d, 1H), 7.08 (t, 1H), 7.30
35 (m, 5H).

90

Example 67B(3aR,9bR)-9-Methoxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole hydrochloride.

The compound resulting from Example 67A as its HCl salt (2.2 g, 6.4 mmol) was dissolved in methanol (150 mL) and 10% Pd/C (0.44 g) was added. The reaction mixture was hydrogenated at 4 atmospheres of hydrogen for 24 hours, filtered, and the solvent evaporated. The product was recrystallized from ethanol:diethyl ether to yield the title compound (1.4 g, 91%) as a white solid. ¹H NMR (300 MHz, CD₃OD) δ 1.60 (m, 1H), 1.88 (m, 1H), 2.53 (m, 1H), 2.80 (m, 2H), 2.88 (dd, 1H), 3.60 (m, 2H), 3.82 (s, 1H), 3.93 (dd, 1H), 6.67 (d, 1H), 6.80 (d, 1H), 7.15 (t, 1H).

Example 67C(3aR,9bR)-9-Methoxy-(2-(4-aminobutyl))-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole

A suspension of the free base of the product from Example 67B (1.95 g, 8.1 mmol), 4-bromobutyronitrile (0.81 mL, 8.1 mmol), and potassium carbonate (1.66g, 12.2 mmol) in acetonitrile was stirred for 18 h at 25 °C. The reaction was partitioned between cold water and EtOAc. The layers are separated and the aqueous layer is extracted with EtOAc (2x). The combined EtOAc layers are washed with brine, dried (MgSO₄), filtered, concentrated, and chromatographed (2 % EtOH in EtOAc) to provide 1.87 g (85 %) of the nitrile intermediate. A solution of the nitrile (1.8 g, 6.7 mmol) in THF was added dropwise to a stirred suspension of lithium aluminum hydride (1.52 g, 40 mmol) in THF (40 mL). After 4 h at 25 °C, a Fieser workup provided 1.8 g of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 1.40 - 1.60 (m, 4H), 1.68 (q, 2H), 1.93 (t, 1H), 2.19 (dd, 1H), 2.40 (t, 2H), 2.50 - 2.67 (m, 3H), 2.70 (t, 2H), 3.11 (dd, 1H), 3.43 (t, 1H), 3.60 (q, 1H), 3.78 (s, 3H), 6.68 (d, 1H), 6.72 (d, 1H), 7.08 (t, 1H): MS (DCI/NH₃).

Example 67D3-[2-((3aR,9bR)-cis-9-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)butyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

2-Carboethoxy-4,5-dimethoxyphenylisocyanate (0.41 g, 1.92 mmol), prepared by the reaction of 2-carboethoxy-4,5-dimethoxyaniline and triphosgene, the product from Example 67C (0.44 g, 1.6 mmol), and toluene (10 mL) were refluxed for 18 h. The reaction was concentrated and redissolved in THF and potassium t-

91

butoxide (4 mL of 1 M solution in THF) was added. After stirring 18 h at 25 °C, the reaction is concentrated and partitioned between NaHCO₃ solution and CH₂Cl₂. The organic layer is dried (MgSO₄), filtered, concentrated, and chromatographed on SiO₂ (10 % EtOH in CH₂Cl₂) and the free base (0.1 g) was converted to the HCl salt: mp 155-160 °C; ¹H NMR (300 MHz, CD₃OD) δ 1.64-1.85 (m, 5H), 1.85-1.95 (m, 1H), 2.68-2.83 (m, 3H), 3.21-3.43 (m, 3H), 3.66-3.78 (m, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.00-4.13 (m, 3H), 6.68 (s, 1H), 6.77 (d, 1H), 6.82 (d, 1H), 7.17 (t, 1H), 7.23 (s, 1H); MS (DCI/NH₃) *m/z* 480 (M+H)⁺. Anal. calcd for C₂₇H₃₄ClN₃O₅·H₂O: C, 60.72; H, 6.79; N, 7.86. Found: C, 60.46; H, 6.67; N, 7.64.

Example 68

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-dimethylquinazoline-2,4(1H,3H)-dione hydrochloride

3,4-Dimethyl-6-carbethoxyaniline, prepared by the method of G.W.Rewcastle *et al.*, *J. Med. Chem.* 34:217 (1991), was treated with 0.33 equivalent of triphosgene. The resulting isocyanate (0.48g, 2.2mmol) and the compound resulting from the example 13J (0.5g, 2mmol) were treated by the procedure described in Example 1C to yield the title compound (0.22g, 24%) as a white solid: mp 185-188 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.6 (s, 1H), 7.1 (t, 1H), 6.76 (d, 1H), 6.68 (s, 1H), 6.65 (d, 2H), 4.25 (t, 2H), 3.81 (s, 3H), 3.62 (m, 2H), 3.48 (m, 1H), 2.7-3.06 (m, 2H), 2.5-2.66 (m, 3H), 2.3 (m, 2H), 2.28 (s, 3H), 2.21 (s, 3H), 1.75 (m, 1H), 1.55 (m, 1H); MS (DCI/NH₃) *m/z* 420 (M+H)⁺. Anal. calcd for C₂₅H₃₀ClN₃O₃·0.75H₂O: C, 63.96; H, 6.76; N, 8.95. Found: C, 64.03; H, 6.56; N, 8.93.

Example 69

3-[2-((3aR,9bR)-cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-carbomethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

Dimethyl 2-aminoterephthalate was treated with 0.33 equivalent triphosgene by the procedure described in the Example 1C. The resulting isocyanate (1.41g, 6mmol) and the compound resulting from Example 13J (1.35g, 5.5mmol) were treated by the procedure described in Example 1C to yield the title compound (1.4g, 57%) as a white solid: mp 228-230 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, 1H), 7.6 (d, 1H), 7.51 (s, 1H), 7.1 (t, 1H), 6.79 (d, 1H), 6.66 (d, 1H), 4.27 (t, 2H), 3.98 (s, 3H), 3.8 (s, 3H), 3.67 (m, 2H), 3.5 (m, 1H), 3.0 (m, *J*=12.5-2.76, m Hz, 3H), 2.33 (m, 2H), 1.8 (m, 1H), 1.6 (m, 1H); MS

92

(DCI/NH₃) *m/z* 450(M+H)⁺. Anal. calcd for C₂₅H₂₈ClN₃O₅•0.25H₂O: C, 61.22; H, 5.86; N, 8.57. Found: C, 61.23; H, 5.79; N, 8.52.

Example 70

5 3-[2-((3a*R*,9b*R*)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-1-yl)ethyl]-7-carboxyquinazoline-2,4(1*H*,3*H*)-dione hydrochloride

The product from Example 69 (0.5g, 1.1mmol) was refluxed for 1 hour with 10 mL of 1N LiOH in 10ml of THF. After acidifying the cooled solution obtain the free base of the title compound which was converted to HCl salt and crystalized from ethanol to yield a white solid (0.4g, 83%): mp >250 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.78 (s, 1H), 8.04 (d, 1H), 7.8 (s, 1H), 7.72 (d, 1H), 7.19 (t, 1H), 6.84 (d, 1H), 6.76 (d, 1H), 4.28 (m, 2H), 3.78 (s, 3H), 3.5 (m, 2H), 3.35 (m, 1H), 3.02 (m, 2H), 2.6-2.82 (m, 3H), 2.45 (m, 2H), 1.78 (m, 1H), 1.61 (m, 1H); MS (DCI/NH₃) *m/z* 436(M+H)⁺. Anal. calcd for C₂₄H₂₆ClN₃O₅•1.5H₂O: C, 57.77; H, 5.86; N, 8.42. Found: C, 57.77; H, 5.88; N, 8.33.

Example 71

20 3-[2-((3a*R*,9b*R*)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-1-yl)ethyl]-7-carboisopropoxyquinazoline-2,4(1*H*,3*H*)-dione hydrochloride

The product from Example 70 (0.28g, 0.64mmol) was refluxed overnight with 30 ml of ethanol and 1ml of H₂SO₄. Solution was evaporated and residue was partitioned in dilute base/CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄ and concentrated to give the free base of the title compound (0.12g, 40%) which was converted to HCl salt and crystalized from ethanol /ether to yield 0.19 g of the title compound as white solid: mp 162-165 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.2 (d, 1H), 8.13 (d, 1H), 7.72 (d, 1H), 7.67 (s, 1H), 7.11 (t, 1H), 7.78 (d, 1H), 6.69 (d, 1H), 4.4 (q, 2H), 4.31 (m, 2H), 3.9 (m, 2H), 3.82 (s, 3H), 3.6-3.8 (m, 1H), 3.0-3.28 (m, 2H), 2.5-2.8 (m, 5H), 1.82 (m, 1H), 1.62 (m, 1H), 1.42 (t, 3H); MS (DCI/NH₃) *m/z* 464(M+H)⁺. Anal. calcd for C₂₆H₃₀ClN₃O₅•H₂O: C, 60.29; H, 6.23; N, 8.11. Found: C, 59.80; H, 6.11; N, 7.81.

93

Example 723-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-carbopropoxyquinazoline-2,4(1H,3H)-dione hydrochloride

The compound from Example 70 (0.35g, 8mmol) was treated with *n*-propanol and 1ml of H₂SO₄ as described in Example 71 to yield after chromatography 0.13g (33%) of title compound as white solid mp 152-155 °C; ¹H NMR (300 MHz, CDCl₃) (free base) δ 8.08 (d, 1H), 7.72 (d, 2H), 7.62 (s, 1H), 7.12 (t, 1H), 6.79 (d, 1H), 6.7 (d, 1H), 4.3 (m, 4H), 3.9 (m, 2H), 3.81 (s, 3H), 3.6 (m, 1H), 3.18 (m, 3H), 2.5-2.8 (m, 5H), 1.82 (m, 3H), 1.6 (m, 1H), 1.08 (t, 2H); MS (DCI/NH₃) *m/z* 478 (M+H)⁺. Anal. calcd for C₂₇H₃₃ClN₃O₅·H₂O: C, 60.95; H, 6.44; N, 7.90. Found: C, 61.08; H, 6.21; N, 7.79.

Example 733-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-carboisopropoxyquinazoline-2,4(1H,3H)-dione hydrochloride

The compound resulting from Example 70 (0.3g, 6.9mmol) was treated with iso-propanol, saturated with HCl as described in Example 71 to yield after chromatography the title compound (0.11g, 33%) as white solid: mp >250 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.16 (d, 1H), 8.13 (s, 1H), 7.79 (d, 1H), 7.53 (s, 1H), 7.12 (t, 1H), 6.76 (d, 1H), 6.71 (d, 1H), 5.23 (m, 1H), 4.38 (m, 2H), 3.9-4.18 (m, 3H), 3.82 (s, 3H), 3.28-3.72 (m, 4H), 2.76 (m, 4H), 2.5-2.66 (m, 1H), 1.88 (m, 1H), 1.62 (m, 1H), 1.4 (s, 3H), 1.38 (s, 3H); MS (DCI/NH₃) *m/z* 478 (M+H)⁺. Analysis calc'd for C₂₇H₃₂ClN₃O₅: C, 63.09; H, 6.27; N, 8.17. Found: C, 62.70; H, 6.17; N, 8.03.

Example 743-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-nitroquinazoline-2,4(1H,3H)-dione hydrochloride

4.74g (22.57mmol) of ethyl 6-amino-4-nitro benzoate, prepared from 2-amino-4-nitrobenzoic acid, was treated with 1.3 equivalent of 2-chloroethylisocyanate by the procedures described in *Eur. J. Med. Chem.*, 28: 499 (1993). The resulting urea (1.23 g, 3.9 mmol) and the compound from Example 13G (0.66 g, 3.25 mmol) were refluxed in 20 mL of acetonitrile in the presence of 0.83 mL of diisopropylethylamine for 48 h. The reaction mixture was evaporated and residue was chromatographed, eluting with ethylacetate:formic acid:water (18:1:1) to afford the free base of the title compound (0.4 g, 29%) which was converted to HCl

94

salt and crystalized from ethanol/ether.: mp >250 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, 1H), 7.72 (m, 2H), 7.09 (t, 1H), 6.68 (d, 1H), 6.65 (d, 1H), 4.3 (m, 2H), 3.8 (s, 3H), 3.42-3.75 (m, 3H), 3.05 (m, 2H), 2.4-2.8 (m, 5H), 1.82 (m, 1H), 1.61 (m, 1H); MS (DCI/NH₃) m/z 437(M+H)⁺. Anal. calcd for C₂₃H₂₅ClN₄O₅·0.5H₂O: C, 57.33; H, 5.44; N, 11.63. Found: C, 57.09; H, 5.11; N, 11.33.

Example 75

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-7-acetamidoquinazoline-2,4(1H,3H)-dione hydrochloride

The compound resulting from Example 74 (0.3g, 0.68mmol) was dissolved in methanol (30 mL) and 10% Pd/C (0.3 g) was added. The reaction was hydrogenated at atmospheric pressure at room temperature for 24 h. The catalyst was removed by filtration and the solvent was evaporated to yield 0.18 g of amino compound. The amino compound (0.15g, 0.37mmol) was dissolved in 25 mL of CH₂Cl₂ and 0.045 mL of pyridine, followed by 0.049 mL (0.44mmol) of acetic anhydride were added to the reaction mixture followed by a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 24 h, the solvents were evaporated and residue chromatographed on SiO₂ to yield the free base of the title compound (0.11g, 66%) which was converted to HCl salt and crystalized from ethanol: mp 255-257 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.88 (d, 2H), 7.08 (t, 1H), 6.85 (d, 1H), 6.75 (d, 1H), 6.69 (d, 1H), 4.25 (m, 2H), 3.8 (s, 3H), 3.6 (m, 2H), 3.48 (m, 1H), 3.0 (m, 2H), 2.5-2.87 (m, 5H), 2.45 (s, 3H), 1.9 (m, 1H), 1.55 (m, 1H); MS (DCI/NH₃) m/z 449(M+H)⁺. Anal. calcd for C₂₅H₂₉ClN₄O₄·H₂O: C, 59.70; H, 6.21; N, 11.14. Found: C, 59.14; H, 5.95; N, 10.97.

Example 76

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-7-methanesulfonylquinazoline-2,4(1H,3H)-dione hydrochloride

1.16g (0.37mmol) of the intermediate urea product obtained by the procedure described for Example 74 was dissolved in 100mL of methanol and hydrogenated for 18 h under 4 atmospheres of pressure in the presence of 0.12 g of Pd/C. Catalyst was removed by filtration and evaporation of solvent yielded the desired amino urea. This compound (1 g, 3.5mmol) was dissolved in 20 mL of CH₂Cl₂, cooled to 0 °C and 0.5 mL of pyridine, followed by 0.3mL (3.87mmol) of methanesulfonyl chloride was added to the reaction mixture. Reaction mixture was stirred at room temperature overnight, then quenched into water and extracted with

95

CH₂Cl₂. Combined organic extracts were evaporated and residue was chromatographed using 30% ethyl acetate:hexane as an eluant. This afforded 0.74g (60%) of desired product. The sulfonamideurea (0.74g, 2 mmol), obtained as described above and 0.47g (2 mmol) of the product from Example 13G were treated as described in Example 74 to yield the title compound (0.31g, 32%) of as a white solid: mp >250 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.22 (s, 1H), 7.82 (d, 1H), 7.08 (t, 1H), 7.02 (d, 1H), 6.92 (dd, 1H), 6.73 (dd, 2H), 3.98 (t, 2H), 3.75 (s, 3H), 3.28 (m, 2H), 3.2 (t, 1H), 3.08 (s, 3H), 2.58 (m, 3H), 2.45 (m, 2H), 2.22 (m, 2H), 1.65 (m, 1H), 1.45 (m, 1H); MS (DCI/NH₃) *m/z* 485(M+H)⁺. Anal. calcd for C₂₄H₂₉ClN₄SO₅: C, 54.39; H, 5.70; N, 10.57. Found: C, 54.46; H, 5.42; N, 10.64.

Example 77

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-7-methoxy-8-methyl-quinazoline-2,4(1H,3H)-dione hydrochloride
2-Methyl-3-nitrophenol (10 g, 65.3 mmol) was refluxed for 4 h in 300 mL of acetone with 2 equivalents of K₂CO₃ (18g) and iodomethane (5mL, 80.31 mmol). The resulting 2-methyl-3-methoxynitrobenzene (9 g, 53.83 mmol) was reduced by hydrogen in the presence of Pd/C (0.9g) in 250mL of methanol. The resulting 2-methyl-3-methoxyaniline was converted to 2-methyl-3-methoxy-6-carbomethoxyaniline as described in *J. Med. Chem.* 34:217 (1991). This was reacted with 0.33 equivalents of triphosgene by the procedure described in Example 1C. The resulting isocyanate (0.43 g, 2.2 mmol) and the compound resulting from the Example 13J (0.5 g, 2 mmol) were treated by the procedures described in Example 1C to yield the title compound (0.5g, 62%) as a white solid: mp 239-240 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.34 (s, 1H), 8.01 (d, 1H), 7.1 (t, 1H), 6.78 (t, 1H), 6.68 (d, 1H), 4.21 (t, 2H), 3.93 (s, 3H), 3.81 (s, 3H), 3.43 (m, 3H), 2.61-2.9 (m, 3H), 2.59 (m, 2H), 2.3 (m, 2H), 1.75 (m, 1H), 1.55 (m, 1H); MS (DCI/NH₃) *m/z* 436(M+H)⁺. Anal. calcd for C₂₅H₃₀ClN₃O₄•0.5H₂O: C, 62.43; H, 6.50; N, 8.74. Found: C, 62.11; H, 6.34; N, 8.59.

Example 78

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol]-1-yl)ethyl]-7-ethoxy-8-methyl-quinazoline-2,4(1H,3H)-dione hydrochloride
2-Methyl-3-ethoxy-6-carbomethoxyaniline was prepared following the procedure described for Example 77 by substituting iodomethane for iodoethane. The product was converted to the corresponding isocyanate by treatment with 0.33

96

equivalents of triphosgene. The resulting isocyanate (0.517 g, 2.2 mmol) and the compound resulting from the Example 13J (0.5g, 2mmol) were treated by the procedures described in Example 1C to yield the title compound (0.45g, 50%) as a white solid: mp 173-175 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.28 (s, 1H), 7.98 (d, 1H), 7.1 (t, 1H), 6.78 (d, 1H), 6.68 (d, 1H), 4.21 (m, 2H), 4.18 (m, 2H), 3.81 (s, 3H), 3.45 (m, 3H), 2.62-2.88 (m, 3H), 2.58 (m, 2H), 2.29 (m, 2H), 2.2 (s, 3H), 1.75 (m, 1H), 1.55 (m, 1H), 1.49 (t, 3H); MS (DCI/NH₃) m/z 450(M+H)⁺. Anal. calcd for C₂₆H₃₂ClN₃O₄·0.5H₂O: C, 63.09; N, 6.72; N, 8.49. Found: C, 62.93; N, 6.68; N, 8.41.

Example 79

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-quinazoline-2,4(1H,3H)-dione hydrochloride

2-Carboethoxy-phenylisocyanate, prepared from 2-carboethoxyaniline (0.33 g, 2.0 mmol) and triphosgene (0.21g, 0.66 mmol) as in Example 1C and the compound resulting from Example 13J were treated by the procedures described in example 1C to yield 0.28 g of title compound as a white solid: mp 170-172 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.96 (d, 1H), 7.5 (t, 1H), 7.1 (m, 2H), 6.9 (d, 1H), 6.88 (d, 1H), 6.68 (d, 1H), 4.26 (t, 2H), 3.81 (s, 3H), 3.4-3.62 (m, 3H), 2.78-3.0 (m, 2H), 2.49-2.77 (m, 3H), 2.3 (m, 2H), 1.77, 1.55 (m, 1H); MS (DCI(NH₃)) m/e 392(M+H)⁺; Analysis calc'd for C₂₃H₂₅N₃O₃·HCl·0.25H₂O: C, 63.88; H, 6.18; N, 9.72; found: C, 63.61; H, 6.09; N, 9.52.

Example 80

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7,8-dimethylquinazoline-2,4(1H,3H)-dione hydrochloride

2,3-Dimethyl-6-carboethoxyaniline, prepared by the method of G.W.Rewcastle et al., J. Med. Chem. 34:217(1991), was treated with 0.33 equivalent of triphosgene. The resulting isocyanate (0.53g, 2.42mmol) and the compound resulting from the example 13J (0.5g, 2mmol) were treated by the procedure described in the example 1C to yield the title compound (0.6g, 70%) as a white solid: m.p. 210-212°; ¹H NMR (300 MHz, CDCl₃(free base)) δ 8.62 (s, 1H), 7.9 (d, 1H), 7.09 (t, 1H), 7.05 (d, 1H), 6.75 (d, 1H), 6.68 (d, 1H), 4.22 (t, 2H), 3.8 (s, 3H), 3.43 (m, 3H), 2.63-2.88 (m, 3H), 2.48-2.6 (m, 2H), 2.39 (s, 3H), 2.28 (m, 2H), 2.26 (s, 3H), 1.73 (m, 1H), 1.52 (m, 1H); MS (DCI(NH₃)) m/e 420(M+H)⁺; Analysis calc'd for C₂₅H₂₉N₃O₃·HCl·H₂O: C, 63.35; H, 6.80; N, 8.86; found: C, 63.18; H, 6.68; N, 8.68.

Example 81**3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7,8-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride**

5 2,3-Dimethoxy-6-carbomethoxyaniline, prepared by the method of G.W.Rewcastle et al., J. Med. Chem.34:217(1991), was treated with 0.33 equivalent of triphosgene. The resulting isocyanate (0.56g,2.4mmol) and the compound resulting from Example 13J (0.48g,1.95 mmol) were treated by the procedure described in Example 1C to yield the title compound (0.5g, 55%) as a
10 white solid: m.p. 174-176°; ¹H NMR (300 MHz, CDCl₃(free base)) δ 8.21 (s, 1H), 7.83 (d, 1H), 7.1 (t, 1H), 6.81 (d, 1H), 6.78 (d, 1H), 6.68 (d, 1H), 4.2 (t, 2H), 3.98 (s, 3H), 3.92 (s, 3H), 3.81 (s, 3H), 3.42 (m, 3H), 2.62-2.88 (m, 3H), 2.55 (m, 2H), 2.28 (m, 2H), 1.78 (m, 1H), 1.52 (m, 1H); MS (DCI(NH₃)) m/e 452(M+H)⁺; Analysis calc'd for C₂₅H₂₉N₃O₅.HCl.H₂O: C, 60.42; H, 6.29; N, 8.45; found: C, 60.87; H, 6.22; N, 8.35.

Example 82**3-[2-((3aR,9bR)cis-6-Ethoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride**

20

Example 82A**(3aR,9bR)-6-Hydroxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole hydrobromide**

25 The product resulting from Example 13G (5g,20.9mmol) was dissolved in 150ml of CH₂Cl₂ and the resulting solution was cooled to -78°C. 21 ml of 1M solution of boron tribromide in methylene chloride was added to the solution and the reaction was warmed to room temperature and stirred for 4 hours. It was cooled again to -78°C and treated with methanol. Evaporation and trituration with ethyl acetate afforded 4.9g (87%) of the title compound as white crystals.

30

Example 82B**(3aR,9bR)-6-Hydroxy-2-carbobenzyloxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole hydrobromide**

35 The product obtained from Example 82A (4.9g, 18.21mmol) was dissolved in 100ml of trifluoroacetic acid. The resulting solution was cooled to 0°C and acetyl chloride (2.58ml,36.42mmol) was added to the reaction mixture. It was stirred at

98

room temperature for 2.5 hours. The reaction mixture was evaporated and partitioned between NaHCO₃ solution and CH₂Cl₂. CBZ chloride (3.8ml, 1.5equiv.) was added to this biphasic solution and it was vigorously stirred for 2 hours.. Then the layers were separated, and the combined organic layers were dried with MgSO₄ and evaporated. The residue was dissolved in ethanol and NH₄OH solution was added to it. The reaction was stirred overnight, then solvents were evaporated and the residue obtained was dissolved in ethyl acetate, washed with water, dil. HCl, and brine. Combined organic layers were dried with MgSO₄ and evaporated to yield 6.9g of the title compound as an oil.

10

Example 82C

(3aR,9bR)-6-Ethoxy-2-carbobenzyloxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[e]isoindole hydrobromide

The product from Example 82B (3.5g, 10.83mmol) was dissolved in 300ml of acetone; 3.0g of K₂CO₃ (2equiv.) and 1.03ml (12.87mmol) iodoethane were added to the solution and it was stirred at reflux for 48 hours.. The reaction mixture was evaporated and the residue was partitioned between water and ethylacetate. The organic layer was separated, dried with MgSO₄ and evaporated. The residue obtained was chromatographed, eluting with 20%ethyl acetate/hexane to afford 2.3g of the title compound.

20

Example 82D

(3aR,9bR)-6-Ethoxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[e]isoindole hydrochloride

The product from Example 82C (2.3 g) was dissolved in 100ml of methanol, 0.23g of Pd/C was added to the solution and it was hydrogenated under 4 atm pressure for 18 hours. The catalyst was removed by filtration and the solvent was evaporated to yield the title compound: ¹H NMR (300 MHz, CDCl₃) δ 7.1 (t, 1H), 6.78 (d, 1H), 6.68 (d, 1H), 4.03 (m, 2H), 3.45 (m, 1H), 3.35 (m, 1H), 3.25 (m, 1H), 2.82 (m, 3H), 2.5 (m, 2H), 1.8 (m, 1H), 1.55 (m, 1H), 1.42 (t, 3H).

25

Example 82E

3aR,9bR)-2-Aminoethyl-6-ethoxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[e]isoindole

The product from Example 82D (1.4g, 6.45mmol) was treated with 0.45ml (1.1equiv.) of chloroacetonitrile as outlined in Example 13I to yield 1.3g of the intermediate nitrile. Reduction with 1.3g of LiAlH₄ as described in Example 13J yielded 1.1g of title compound.: ¹H NMR (300 MHz, CDCl₃) δ 7.09 (t, 1H), 6.73

30

35

99

(d, 1H), 6.68 (d, 1H), 4.02 (q, 2H), 3.42 (m, 1H), 3.28 (m, 2H), 2.8 (t, 2H), 2.48-2.78 (m, 5H), 2.18 (t, 2H), 1.71 (m, 1H), 1.55 (m, 1H).

Example 82F

5 3-[2-((3aR,9bR)cis-6-Ethoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

2-Carbomethoxy-4,5,-dimethoxylamine was treated with 0.33 equivalent of triphosgene. The resulting isocyanate (0.33g, 1.39mmol) and the compound resulting from Example 82E (0.3g, 1.15mmol) were treated by the procedures described in
 10 Example 1C to yield 0.28g (52%) of title compound as a white solid.: m.p. 220-222°; ¹H NMR (300 MHz, CDCl₃) δ 7.09 (d, 1H), 7.05 (s, 1H), 6.75 (d, 1H), 6.68 (d, 1H), 6.15 (s, 1H), 4.29 (m, 2H), 4.02 (q, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 3.78 (m, 2H), 3.52 (q, 2H), 3.15 (m, 1H), 3 (om, 1H), 2.55-2.8 (m, 3H), 2.35 (q, 2H), 1.81 (m, 1H), 1.58 (m, 1H), 1.42 (t, 3H); MS (DCI(NH₃)) m/e 466
 15 (M+H)⁺; Analysis calc'd for C₂₆H₃₁N₃O₅.HCl.H₂O: C, 60.05; H, 6.59; N, 8.08; found: C, 59.74; H, 6.40; N, 7.93.

Example 83

20 3-[2-((3aR,9bR)cis-6-Ethyl-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride

Example 83A

(3aR,9bR)-6-Hydroxy-2-carbobenzoyloxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole trifluoromethanesulfonate ester

25 To a stirred solution of the product from Example 82B, (0.385g., 1.2 mMol., 1.0 equiv.) in 12mL CH₂Cl₂ cooled to -78° was added triethylamine, (0.17 mL, 1.2 mMol., 1.0 equiv.) followed by trifluoromethanesulfonic anhydride, (0.17 mL, 1.2 mMol., 1.0 equiv.). The reaction solution was left stirring at -78° for 1h when it was warmed to room temperature, diluted with 50 mL CH₂Cl₂ and washed
 30 with H₂O, (15 mL), followed by sat. NaHCO₃. The resulting solution was then dried over MgSO₄, filtered, and solvents evaporated to furnish the crude product as an oil. Purification of the crude product on silica gel furnished the title compound as a colorless oil, (0.39g, 70%) ¹H NMR (300 MHz, CDCl₃), δ(TMS): 1.60, (1H, m); 1.92, (1H, m); 2.50, (1H, m), 2.67, (1H, m); 3.00, (1/2 H, t, J = 3.0 Hz);
 35 3.05, (1/2 H, t, J = 3.0 Hz); 3.23, (1H, q, J = 9.0 Hz); 3.45, (2H, m); 3.73, (1H, dd, J = 6.0 Hz); 3.98, (1H, m); 5.13, (2H, m); 7.15, 3H, m); 7.34, (5H, m).

Example 83B(3aR,9bR)-6-Acetyl-2-carbobenzyloxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole

5 To a stirred solution of the product from Example 83A (0.385g, 0.85 mMol., 1.0 equiv.), in 3 mL of DMF was added triethylamine, (0.355 mL, 0.255 mMol., 3.0 equiv.), butylvinyl ether, (0.821 mL, 5.9 mMol., 7.0 equiv.), 1, 3-bis(diphenylphosphino)propane, (0.05g , 0.12 mMol., 0.15 equiv.) and palladium(II)acetate, (0.02g , 0.12 mMol., 0.15 equiv.). The resulting dark reaction
10 solution was heated to 80°C for 2h when it was cooled to room temperature and quenched with 5% (v/v) HCl, (2mL), and let stir at room temperature for 2h. The reaction was then extracted with CH₂Cl₂ (3 x 30mL), and the resulting combined organics washed with H₂O, and brine, dried over MgSO₄, filtered and evaporated and separated (silica gel, 5:1 hexanes/ ethyl acetate), to furnish the title compound as
15 a colorless oil, (0.18g, 61%). ¹H NMR (300 MHz, CDCl₃), δ(TMS): 1.54, (1H, m); 1.86, (1H, m); 2.45, (1H, m), 2.55, (3H, s); 2.90, (1H, m); 3.07, (1H, m); 3.25, (1H, q, J = 9.0 Hz); 3.45, (2H, m); 3.73, (1H, dd, J = 6.0 Hz); 4.00, (1H, m); 5.13, (2H, m); 7.22, (2H, m); 7.34, (5H, m); 7.52, (1H,m).

20

Example 83C(3aR,9bR)-6-Ethyl-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole hydrochloride

The product from Example 83B (0.30g, .085 mMol., 1.0 equiv.) was dissolved in 25 mL of dry methanol to which was added 1 mL of conc. HCl. To this solution was added dry 10% Pd/C, (0.045g), the resulting suspension was then put
25 under a hydrogen atmosphere at 4 atmospheres pressure for 17 h at room temperature. The reaction suspension was then filtered and evaporated to give a crude solid which was triturated with methanol / diethyl ether to furnish the title compound, (0.172g, 78%). ¹H NMR (300 MHz, CDCl₃), δ(TMS): 1.17, (3H, t, J = 7.5 Hz); 1.63, (1H, m); 1.95, (1H, m), 2.63, (4H, m); 2.90, (1H, m); 3.07,
30 (1H, t, J = 12 Hz); 3.22, (1H, dd, J = 9.0 Hz, J = 3Hz); 3.77, (1H, dd, J = 12.0 Hz, J = 3.0Hz); 7.07, (3H, m).

Example 83D(3aR,9bR)-2-Cyanomethyl-6-ethyl-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole

The product from Example 83C (1.23g, 5.2 mmol), chloroacetonitrile (0.22
35 mL, 5.7 mmol), potassium carbonate (2.4 g, 11.4 mmol), acetone (30 mL), and water (10 mL) were stirred at reflux for 6 h. The reaction was partitioned between

101

ethyl acetate and brine. The ethyl acetate layer was dried (MgSO₄), filtered, concentrated and chromatographed (2:1 hex:ethyl acetate) to yield 1.0 g (80 %) of the title compound ¹H NMR (300 MHz, CDCl₃) δ 1.20 (t, 3H), 1.61-1.71 (m, 1H), 1.76-1.87 (m, 1H), 2.50-2.79 (m, 7H), 3.20-3.28 (m, 2H), 3.50 (q, 1H), 3.65 (s, 2H), 6.97 (d, 1H), 7.03 (d, 1H), 7.11 (t, 1H); MS (DCI/NH₃) *m/e* 241 (M+H)⁺.

Example 83E**(3aR,9bR)-2-Aminoethyl-6-ethyl-2,3,3a,4,5,9b-[1H]-hexahydrobenz[elisoindole**

The product from Example 83D (1.0 g, 4.2 mmol) in 20 mL THF was added dropwise to a suspension of LiAlH₄ (0.93 g, 25 mmol) in THF (80 mL). After stirring for 1 h, the reaction was quenched by the portionwise addition of sodium sulfate decahydrate. After stirring for 30 min, the reaction was diluted with ethyl acetate (100 mL) and the solid was removed by filtration. Concentration of the filtrate yielded 0.97 g (95 %) of the title compound: ¹H NMR (300 MHz, CDCl₃) δ 1.19 (t, 3H), 1.47-1.84 (m, 4H), 2.14-2.22 (m, 2H), 2.45-2.74 (m, 6H), 2.81 (t, 2H), 3.22-3.33 (m, 2H), 3.45 (q, 1H), 4.15-4.27 (m, 1H), 6.95-7.13 (m, 3H); MS (DCI/NH₃) *m/e* 245 (M+H)⁺.

Example 83F**3-[2-((3aR,9bR)-cis-6-Ethyl-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione hydrochloride**

Following the procedure described in Example 1C, methyl 2-amino-4,5-dimethoxybenzoate (0.24 g, 1.1 mmol), Et₃N (0.36 mL, 2.6 mmol), phosgene (0.59 mL of 1.93 M solution in toluene), and the product from Example 83E (.25 g, 1.0 mmol) provided 0.20 g (44 %) of the free base of the title compound which was converted to the HCl salt: mp 200-202 °C; ¹H NMR (300 MHz, CDCl₃(free base)) δ 1.19 (t, 3H), 1.53-1.69 (m, 1H), 1.78-1.89 (m, 1H), 2.34 (q, 2H), 2.54-2.80 (m, 5H), 2.95-3.06 (m, 1H), 3.14-3.26 (m, 1H), 3.57 (m, 1H), 3.78-3.91 (m, 2H), 3.84 (s, 3H), 3.97 (s, 3H), 4.19-4.39 (m, 2H), 6.14 (s, 1H), 6.96-7.13 (m, 3H), 7.00 (s, 1H), 11.30 (bs, 1H); MS (DCI/NH₃) *m/z* 450 (M+H)⁺. Anal. calcd for C₂₆H₃₂ClN₃O₄•0.25 H₂O: C, 63.67; H, 6.68; N, 8.57. Found: C, 64.26; H, 6.64; N, 8.65.

102

Example 84

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-(2-methylphenyl)thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione
hydrochloride

- 5 Ethyl 3-amino-4-(2-methylphenyl)thiophene-2-carboxylate (0.81 g, 3.10 mmol) was dissolved in 30 mL dichloromethane and cooled to -78 °C. Triethylamine (0.69 mL, 4.95 mmol) was then added, followed by the dropwise addition of 1.27 mL (2.45 mmol) 1.93 M phosgene in toluene solution. The reaction was stirred at -78° C for 1 h and then allowed to warm to rt, at which time a solution of the product from Example 13J (0.61 g, 2.45 mmol) in 15 mL dichloromethane was added. The reaction was stirred at room temperature for 2 h., quenched in 5% NaHCO₃, extracted with dichloromethane (3x), and the combined extracts washed with brine, dried (Na₂SO₄), filtered, and evaporated. The resulting oil (1.18 g) was taken up in 50 mL of anhydrous tetrahydrofuran and 0.30 g (2.36 mmol) anhydrous potassium *t*-butoxide added. The reaction was stirred 2 h at room temperature, then quenched in 100 mL of pH 7 buffer solution, extracted with ethyl acetate, dried (Na₂SO₄), and evaporated. The resulting product was treated with ethereal HCl to yield 0.44 g of the title compound as a white solid.: mp 197-200 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.6 (m, 2H), 1.8 (m, 2H), 2.65 (m, 3H), 3.0 (m, 2H), 3.35 (s, 3H), 3.45-3.55 (m, 3H), 3.78 (s, 3H), 4.0-4.25 (m, 2H), 6.7-6.87 (m, 2H), 7.1-7.4 (m, 6H), 7.78 (d, 1H), 11.65 (d, 1H); MS (DCI/NH₃) *m/e* 488 (M+H)⁺. Anal. calcd for C₂₈H₃₀ClN₃O₃S•0.25H₂O: C, 63.62; H, 5.82; N, 7.95. Found: C, 63.49; H, 5.58; N, 7.59.

Example 85

- 25 3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-7-(2-methoxyphenyl)thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione
hydrochloride

- 30 Ethyl 3-amino-2,4-(2-methoxyphenyl)thiophene-2-carboxylate (0.86 g, 3.10 mmol) was dissolved in 30 mL dichloromethane and cooled to -78°C. 0.69 ml (4.95 mmol) of triethylamine was then added, followed by the dropwise addition of 1.27 mL (2.45 mmol) 1.93 M phosgene in toluene solution. The reaction was stirred at -78° C for 1h and then allowed to warm to room temperature, at which time a solution of the the product from Example 13J (0.61 g, 2.45 mmol) in 15 mL dichloromethane was added. The reaction was stirred at rt for 2 h and then quenched in 5% NaHCO₃, extracted with CH₂Cl₂, dried (Na₂SO₄), filtered, and evaporated. The resulting solid (1.08 g) was taken up in 50 mL of anhydrous tetrahydrofuran

103

and 0.26 g (2.36 mmol) anhydrous potassium *t*-butoxide added. The reaction was stirred 2 h at room temperature, then quenched in 100 mL of pH 7 buffer solution. The reaction was extracted with ethyl acetate, dried (Na₂SO₄), and evaporated. The resulting product was treated with ethereal HCl to yield 0.64 g of the title compound as a white solid: mp 228-230 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.6 (m, 1H), 1.8 (m, 1H), 2.4-3.05 (m, 4H), 3.4-3.9 (m, 4H), 3.8 (s, 6H), 4.0-4.3 (m, 4H), 6.7-6.87 (m, 2H), 7.0-7.25 (m, 4H), 7.42 (t, 1H), 7.78 (s, 1H), 10.5 (d, 1H), 11.4 (d, 1H); MS (DCI/NH₃) *m/z* 504 (M+H)⁺. Anal. calcd for C₂₈H₃₀ClN₃O₄S•0.25H₂O: C, 61.76; H, 5.65; N, 7.72. Found: C, 61.81; H, 5.58; N, 7.59.

Example 86

3-[2-((3a*R*,9b*R*)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*ef*]isoindol-1-yl)ethyl]-7,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione hydrochloride
Methyl 2,3-dimethyl-4-amino-pyridine-5-carboxylate (0.27 g, 1.50 mmol) was dissolved in 10 mL dichloromethane and cooled to -78 °C. Triethylamine (0.42 mL, 3.00 mmol) was then added, followed by the dropwise addition of 0.78 mL (1.50 mmol) 1.93 M phosgene in toluene solution. The reaction was stirred at -78° C for 1h and then allowed to warm to room temperature, at which time a solution of the the product from Example 13J (0.50 g, 1.8 mmol) in 5 mL dichloromethane was added. The reaction was stirred at rt for 2 h and then quenched in 5% NaHCO₃, extracted with CH₂Cl₂, dried (Na₂SO₄), filtered, and evaporated. The resulting solid (0.42 g) was taken up in 30 mL of anhydrous tetrahydrofuran and 0.16 g (1.50 mmol) anhydrous potassium *t*-butoxide added. The reaction was stirred 2 h at room temperature, then quenched in 100 mL of pH 7 buffer solution. The reaction was extracted with ethyl acetate, dried (Na₂SO₄), and evaporated. The resulting product was treated with methanolic HCl to yield 0.23 g of the title compound as a white solid: mp 219-225 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.6 (m, 1H), 1.8 (m, 1H), 2.4-3.1 (m, 2H), 2.5 (d, 6H), 3.3-3.7 (m, 4H), 3.8 (s, 6H), 3.9-4.3 (m, 4H), 6.7-6.87 (m, 2H), 7.15 (t, 1H), 8.95 (s, 1H), 11.25 (d, 1H), 11.8 (s, 1H); MS (DCI/NH₃) *m/z* 421. Anal. calcd for C₂₄H₃₀Cl₂N₄O₃•H₂O: C, 56.36; H, 6.31; N, 10.95. Found: C, 56.19; H, 6.40; N, 10.83.

104

Example 87

3-[2-((3a*R*, 9b*R*)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-1-yl)ethyl]-2,4-pteridinedione hydrochloride

5

Example 87AMethyl 3-(*N*-(2-chloroethyl)carbamido)-2-pyrazinecarboxylate

Methyl 3-amino-2-pyrazinecarboxylate (10g, 65.2 mmol) was dissolved in 200 mL anhydrous toluene, 2-chloroethyl isocyanate (5.6mL, 65.2 mmol) was added and the mixture was heated to gentle reflux. After 1.25 h, more 2-chloroethyl isocyanate (2.78 mL, 32.6 mmol) was added and the mixture was heated to 60 °C overnight. The mixture was evaporated to a brown solid, then purified by column chromatography on silica gel eluting with a gradient of diethyl ether, 30:70 ethyl acetate:hexane, and ethyl acetate to give 1.1g (6%) of the title compound as a white solid mp 122-124 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.52 (dd, 2H), 3.72 (t, 2H), 3.89 (s, 3H), 8.36 (d, 1H), 8.53 (d, 1H), 9.81 (s, 1H); MS (DCI/NH₃) 259 (M+H)⁺.

15

Example 87B

3-[2-((3a*R*, 9b*R*)*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1*H*]-benz[*e*]isoindol-1-yl)ethyl]-2,4-pteridinedione hydrochloride

The product from Example 87A (0.264 g, 1.02 mmol) was combined with *N,N'*-diisopropylethylamine (0.533 mL, 3.06 mmol) and 0.245 g (1.02 mmol) of the compound resulting from Example 13J in 15 mL anhydrous toluene, then heated to 70 °C overnight. The mixture was evaporated to a brown solid, then purified by column chromatography on silica gel eluting with a gradient of 5:5:90 water:formic acid:ethyl acetate, then 10:10:80 water:formic acid:ethyl acetate, evaporated with an excess of HCl/methanol, then heated to reflux in ethanol and filtered to give 0.041g (10%) of the title compound as a white solid: mp 310-312 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.47 (m, 1H), 1.62 (m, 1H), 2.11-2.28 (m, 2H), 2.4-2.68 (m, 6H), 3.18-3.31 (m, 3H), 3.76 (s, 3H), 4.0 (t, 2H), 6.72 (d, 2H), 7.09 (t, 1H), 8.36 (d, 1H), 8.65 (d, 1H); HRMS calcd for C₂₁H₂₄N₅O₃: 394.1893; found: 394.1879. Anal. calcd for C₂₁H₂₄ClN₅O₃•1.5 H₂O: C, 55.20; H, 5.96; N, 15.33. Found: C, 55.23; H, 5.32; N, 14.98.

30

105

Example 88

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-pyrimidinol[4,5-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

5

Example 88AEthyl 4-(N-(2-chloroethyl)carbamido)-5-pyrimidinecarboxylate

Ethyl 5-amino-6-pyrimidinecarboxylate (1.0g; 6.54 mmol) was combined with 2-chloroethyl isocyanate (0.834 ml, 9.81 mmol) in 65 mL anhydrous toluene and heated to reflux overnight. The mixture was evaporated to a white solid, then
10 purified by column chromatography on silica gel eluting with 1:1 hexanes:ethyl acetate to give 0.69g (41%) of the title compound as a white solid: mp 115-118 °C; ¹H NMR (300 MHz DMSO-*d*₆) δ 3.61 (dd 2H), 3.76 (t, 2H), 3.91 (s, 3H), 8.96 (s, 1H), 9.05 (s, 1H), 9.28 (br t, 1H), 9.91 (s, 1H); MS (DCI/NH₃) *m/z* 258 (M+H)⁺.

15

Example 88B

3-[2-((3aR,9bR)cis-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[elisoindol-1-yl)ethyl]-pyrimidinol[4,5-d]pyrimidine-2,4(1H,3H)-dione hydrochloride

The product from Example 88A (0.232g, 0.897 mmol) was combined with *N,N'*-diisopropylethylamine (0.312 mL, 1.79 mmol), and 0.215 g (0.897 mmol)
20 of the compound resulting from Example 13J in 10 ml CH₃CN; then heated to 70°C overnight. The mixture was evaporated, then purified by column chromatography on silica gel eluting with a gradient of 1:1:30 water:formic acid:ethyl acetate, then 5:5:90, then 10:10:90 in a sequential manner. The resulting homogeneous product was evaporated with an excess of HCl-methanol to produce 0.085 g of the title
25 compound as a white solid: mp 277-279 °C; ¹H NMR (300 MHz DMSO-*d*₆) δ 1.6 (m, 1H), 1.78 (m, 1H), 2.6-2.76 (m, 2H), 2.98-3.06 (m, 1H), 3.44-3.52 (m, 3H), 3.78 (s, 1H), 3.90-4.26 (m, 5H), 6.71-6.86 (m, 2H), 7.18 (t, 1H), 9.11 (m, 2H), 12.58 (br s, 1H); MS (DCI/NH₃) 394 (M+H)⁺. Anal. calcd for C₂₁H₂₈ClN₅O₃•1.5 H₂O: C, 55.20; H, 5.96; N, 15.33. Found C, 54.85; H, 5.56; N, 15.15.
30

Example 89-118

The following compounds can be prepared by the procedures described in the preceding examples and schemes.

Example	Name
89	2-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1,2,3,4-tetrahydroisoquinolin-1,3-dione
90	2-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline
91	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-2,4-pteridinedione
92	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-(3,4-dimethoxyphenyl)-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione
93	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione
94	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-chloro-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione
95	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-6-dimethylaminocarbonyl-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione
96	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-oxazolo[5,4-d]pyrimidine-5,7(4H,6H)-dione
97	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-amino-oxazolo[5,4-d]pyrimidin-5(6H)-one
98	1-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-3,9-dimethyl-[1H]-purine-2,6-dione
99	1-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-3,7-dimethyl-[7H]-imidazo[4,5-d]pyrimidin-2,6-dione
100	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-methoxy-quinazoline-2,4(1H,3H)-dione
101	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7,8-ethylenedioxy-quinazoline-2,4(1H,3H)-dione
102	3-[2-(<i>cis</i> -6-Hydroxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione

103	2-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-4-amino-6,7-dimethoxy-quinazoline
104	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-chloro-7-methoxy-quinazoline-2,4(1H,3H)-dione
105	3-[2-(<i>cis</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-cyano-quinazoline-2,4(1H,3H)-dione
106	3-[2-(<i>trans</i> -9-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-[1H,3H]-quinazoline-2,4(1H,3H)-dione
107	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione
108	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-8-methoxy-quinazoline-2,4(1H,3H)-dione
109	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione
110	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-chloro-quinazoline-2,4(1H,3H)-dione
111	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbomethoxy-quinazoline-2,4(1H,3H)-dione
112	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7,8-trimethoxy-quinazoline-2,4(1H,3H)-dione
113	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-quinazoline-2,4(1H,3H)-dione
114	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-4(3H)-one
115	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione
116	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-ethylenedioxyquinazoline-2,4(1H,3H)-dione
117	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methyl-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione
118	3-[2-(<i>trans</i> -6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione

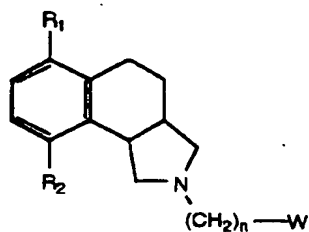
108

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

109

WE CLAIM:

1. A compound of the formula:



5

or a pharmaceutically acceptable salt thereof wherein

 n is an integer from 2 to 6; R_1 and R_2 are independently selected from the group consisting of

hydrogen,

alkyl of one to six carbon atom,

10

alkoxy of one to six carbon atoms,

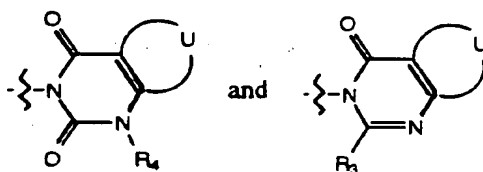
hydroxy,

halo,

carboxy, and

alkoxycarbonyl of two to eight carbon atoms;

15

 W is selected from the group consisting of

20

25

110

wherein R₃ is selected from the group consisting of
hydrogen,

30

alkyl of one to six carbon atoms,

unsubstituted phenyl and

phenyl substituted with

alkyl of one to six carbon atoms, and

R₄ is hydrogen or alkyl of one to six carbon atoms;

35

and

U, taken together with the carbon atoms to which it is attached forms
a ring selected from the group consisting of

40

- (a) a fused unsubstituted or substituted five membered
ring having four carbon atoms, two double bonds and
one heteroatom selected from the group consisting of
-N(R₅)-, -O- and -S- wherein R₅ is hydrogen or alkyl
of one to six carbon atoms and the ring substituent is
selected from the group consisting of alkyl of one to
six carbon atoms, phenyl, halo, cyano, nitro,
carboxy, alkoxycarbonyl of two to eight carbon atoms
and alkoxy of one to six carbon atoms;

45

50

- (b) a fused unsubstituted or substituted five membered
ring having three carbon atoms, two double bonds
and two heteroatoms selected from the group
consisting of two nitrogen atoms, one oxygen atom
and one nitrogen atom, and one sulfur atom and one
nitrogen atom wherein the ring substituent is selected
from the group consisting of alkyl of one to six
carbon atoms, phenyl, halo, cyano, nitro, carboxy,
alkoxycarbonyl of two to eight carbon atoms and
alkoxy of one to six carbon atoms;

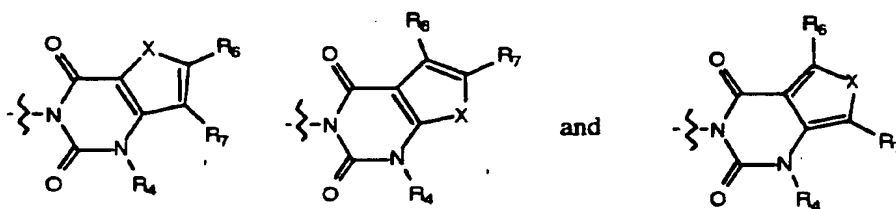
55

60

111

- 65 (c) a fused benzene ring which is unsubstituted or substituted with alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms methylenedioxy and ethylenedioxy; and
- 70 (d) an unsubstituted or substituted fused six membered ring having one to three double bonds and one or two nitrogen atoms, wherein the ring substituents are selected from the group consisting of alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro,
- 75 carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms.

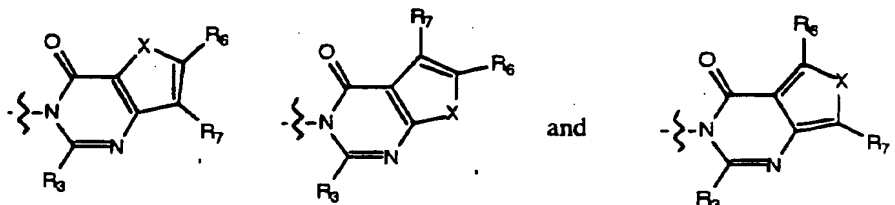
2. A compound according to Claim 1 wherein W is selected from the group consisting of



- wherein X is selected from the group consisting of -N(R₅)-, -O- and -S- wherein R₅ is hydrogen or alkyl of one to six carbon atoms, and R₆ and R₇ are the same or different and are independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms, and alkoxy of one to six carbon atoms.
- 10
- 15

112

3. A compound according to Claim 1 wherein W is selected from the group consisting of

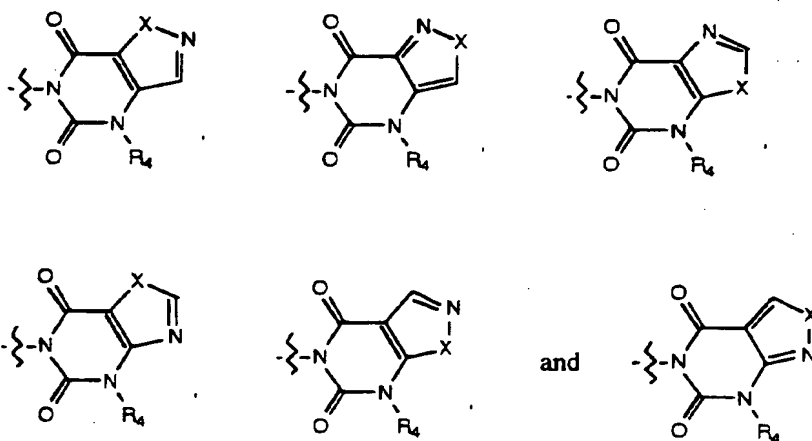


5

wherein X is selected from the group consisting of -N(R₅)-, -O- and -S- wherein R₅ is hydrogen or alkyl of one to six carbon atoms, and R₆ and R₇ are the same or different and are independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms, and alkoxy of one to six carbon atoms.

10

4. A compound according to Claim 1 wherein W is selected from the group consisting of

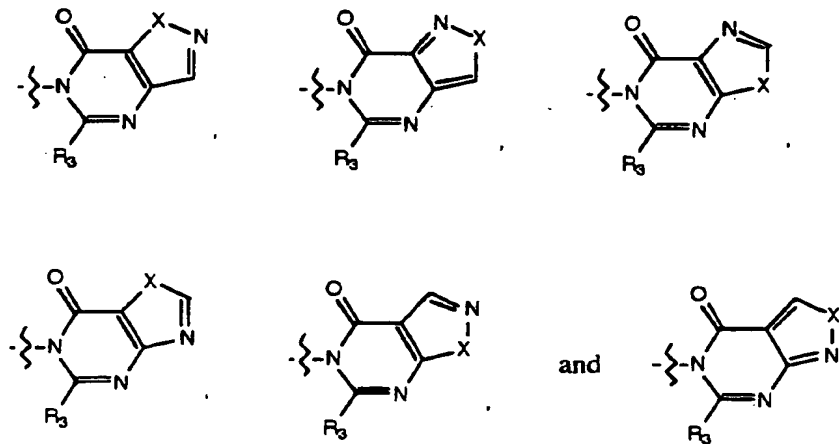


5

wherein X is selected from the group consisting of -N(R₅)-, -O- and -S- wherein R₅ is hydrogen or alkyl of one to six carbon atoms.

113

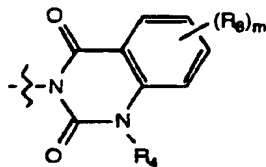
5. A compound according to Claim 1 wherein W is selected from the group consisting of



5

wherein X is selected from the group consisting of $-N(R_5)-$, $-O-$ and $-S-$ wherein R_5 is hydrogen or alkyl of one to six carbon atoms.

6. A compound according to Claim 1 wherein W is



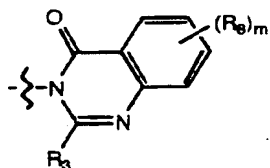
5

wherein m is selected from 1, 2 and 3 and, when m is 2 or 3, R_8 at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxy, carbonyl of two to eight carbon atoms, alkoxy of one to six carbon atoms and, when m is 2, methylenedioxy and ethylenedioxy.

10

114

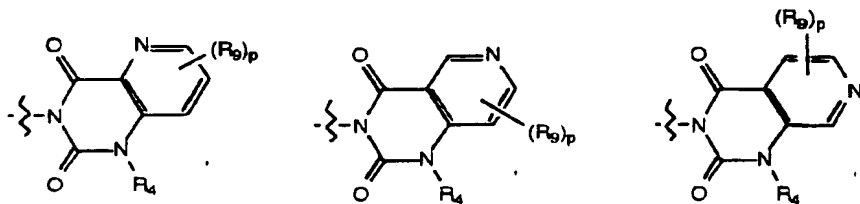
7. A compound according to Claim 1 wherein W is



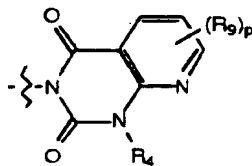
- 5 wherein m is selected from 1, 2 and 3 and, when m is 2 or 3, R₉ at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxy carbonyl of two to eight carbon atoms, alkoxy of one to six carbon atoms and, when m is 2, methylenedioxy and ethylenedioxy..

10

8. A compound according to Claim 1 wherein W is selected from the group consisting of



and



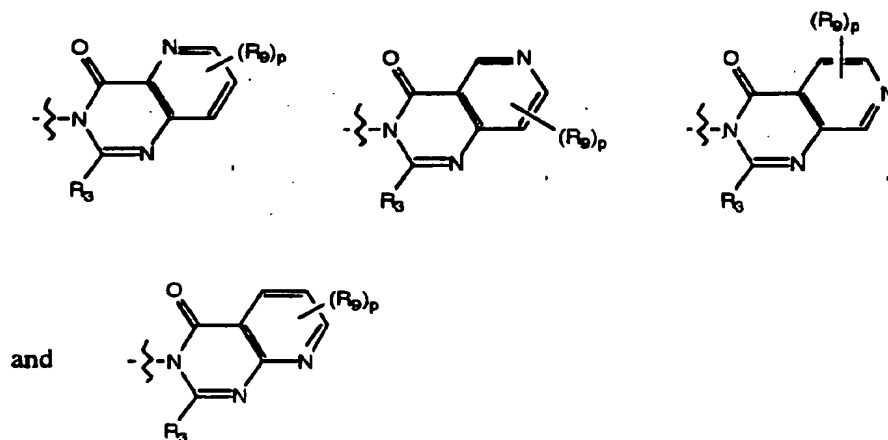
5

- wherein p is selected from 1 and 2 and, when p is 2, R₉ at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxy carbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms.

10

115

9. A compound according to Claim 1 wherein W is selected from the group consisting of

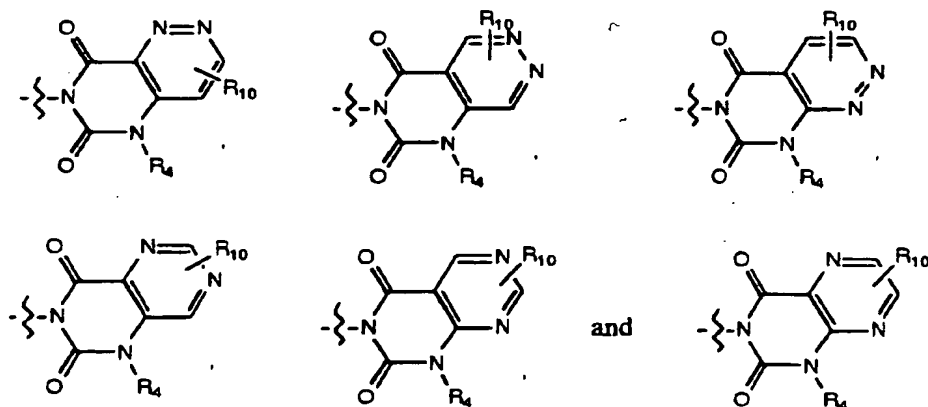


5

wherein p is 1 or 2 and, when p is 2, R_9 at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms.

10

10. A compound according to Claim 1 wherein W is selected from the group consisting of

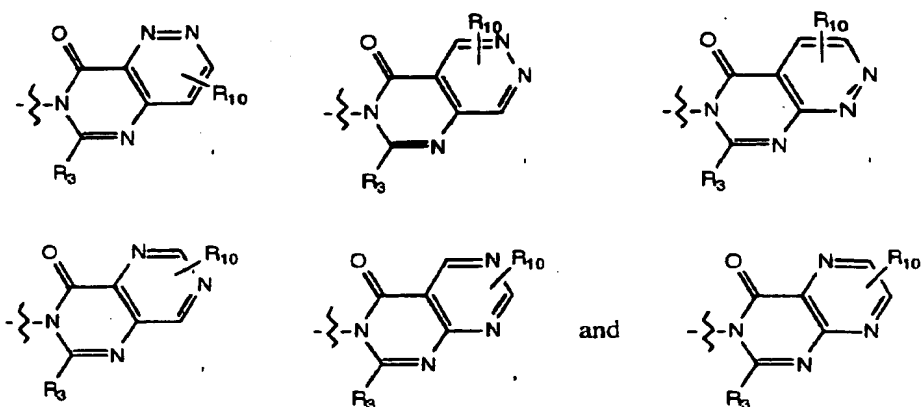


5

116

wherein R_{10} is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms.

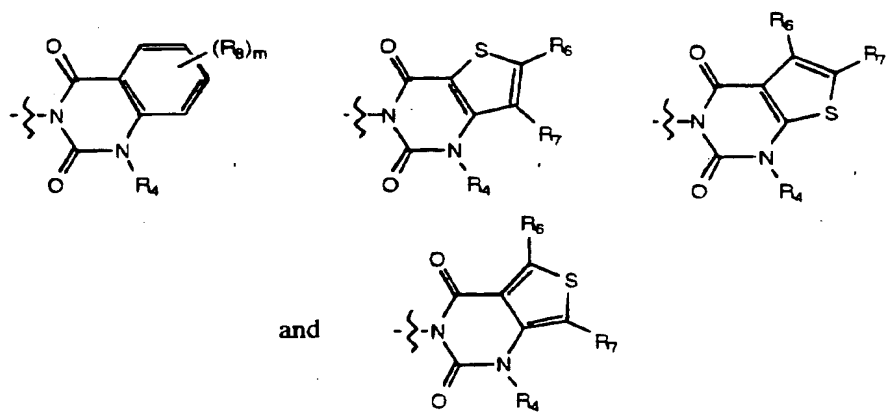
11. A compound according to Claim 1 wherein W is selected from the group consisting of



5

wherein R_{10} is selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxycarbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms.

12. A compound according to Claim 1 wherein W is selected from the group consisting of



5

wherein m is selected from 1, 2 and 3 and, when m is 2 or 3, R₈ at each occurrence is independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, halo, cyano, nitro, carboxy, alkoxy, alkoxy carbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms and, when m is 2, methylenedioxy and ethylenedioxy, and R₆ and R₇ are the same or different and are independently selected from the group consisting of hydrogen, alkyl of one to six carbon atoms, phenyl, halo, cyano, nitro, carboxy, alkoxy carbonyl of two to eight carbon atoms and alkoxy of one to six carbon atoms.

13. A compound according to Claim 1 selected from the group consisting of:
- 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-8-methoxy-quinazoline-2,4(1H,3H)-dione;
 - 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxy-quinazoline-2,4(1H,3H)-dione;
 - 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-chloro-quinazoline-2,4(1H,3H)-dione;
 - 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-thieno[2,3-d]pyrimidine-2,4(1H,3H)-dione;
 - 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-7-carbomethoxy-quinazoline-2,4(1H,3H)-dione;
 - 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6-methoxy-quinazoline-2,4(1H,3H)-dione;
 - 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,8-dimethyl-quinazoline-2,4(1H,3H)-dione;
 - 3-[2-(*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-1-methylquinazoline-2,4(1H,3H)-dione;
 - 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-2,4(1H,3H)-dione;
 - 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-ethylenedioxyquinazoline-2,4(1H,3H)-dione;
 - 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-

dione;

- 30 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-4(1H,3H)-
one;
- 3-[2-(*cis*-6-hydroxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-1-
yl)ethyl]-thieno[2,3-d]pyrimidine-4(1H,3H)-one;
- 35 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-1-methyl-7-methoxyquinazoline-
2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-1-(2-methoxyethyl)-6,7-
dimethoxyquinazoline-2,4(1H,3H)-dione;
- 40 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7,8-methylenedioxyquinazoline-
2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-6,7-methylenedioxyquinazoline-
2,4(1H,3H)-dione;
- 45 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-6,7-dimethoxyquinazoline-4(3H)-one;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7,8-dimethoxyquinazoline-4(3H)-one;
- 50 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7,8-dimethylpyrido[3,2-d]pyrimidine-
2,4(1H,3H)-dione;
- 3-[2-((3aR,9bR)-*cis*-9-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)butyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-
dione;
- 55 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7-carbomethoxyquinazoline-2,4(1H,3H)-
dione;
- 3-[2-((3aR,9bR)-*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7-carboisopropoxyquinazoline-
2,4(1H,3H)-dione;
- 60

119

- 3-[2-((3a*R*,9b*R*)*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7-carbopropoxyquinazoline-2,4(1H,3H)-
dione;
- 65 3-[2-((3a*R*,9b*R*)*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7-nitroquinazoline-2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7-methoxy-8-methyl-quinazoline-
2,4(1H,3H)-dione;
- 70 3-[2-((3a*R*,9b*R*)*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7-ethoxy-8-methyl-quinazoline-
2,4(1H,3H)-dione;
- 3-[2-((3a*R*,9b*R*)*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7,8-dimethylquinazoline-2,4(1H,3H)-
dione;
- 75 3-[2-((3a*R*,9b*R*)*cis*-6-methoxy-2,3,3a,4,5,9b-hexahydro-[1H]-
benz[e]isoindol-1-yl)ethyl]-7,8-dimethoxyquinazoline-2,4(1H,3H)-
dione;
- 3-[2-((3a*R*,9b*R*)*cis*-6-ethoxy-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-
1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione; and
- 80 3-[2-((3a*R*,9b*R*)*cis*-6-Ethyl-2,3,3a,4,5,9b-hexahydro-[1H]-benz[e]isoindol-
1-yl)ethyl]-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione;
- or a pharmaceutically acceptable salt thereof.
14. A pharmaceutical composition comprising a therapeutically effective
amount of a compound of Claim 1 in combination with a pharmaceutically
acceptable carrier.
15. A method of treating benign prostatic hyperplasia (BPH) in a host mammal
in need of such treatment comprising administering a therapeutically effective
amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

CT/US 96/00178

A. CLASSIFICATION F SUBJECT MATTER

IPC 6 C07D487/02 A61K31/505 C07D495/02 C07D475/02 C07D487/00
 //(C07D487/00,239:00,209:00),(C07D495/02,333:00,239:00,209:00),
 (C07D487/02,239:00,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 12754 (ABBOTT LAB) 8 July 1993 see the whole document ---	1-14
Y	EP,A,0 095 666 (ABBOTT LAB) 7 December 1983 see the whole document ---	1-14
Y	WO,A,89 06645 (ABBOTT LAB) 27 July 1989 see the whole document ---	1-14
Y	WO,A,89 06534 (ABBOTT LAB) 27 July 1989 see the whole document ---	1-14
Y	EP,A,0 325 963 (ABBOTT LAB) 2 August 1989 see the whole document ---	1-14
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 June 1996

Date of mailing of the international search report

28.06.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx 31 651 epo nl,
 Fax (+ 31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No

:T/US 96/00178

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,5 158 953 (CHERN JI-WANG ET AL) 27 October 1992 see the whole document ---	1-14
Y	J. PHARMACOL. EXP. THER., vol. 242, no. 1, 1987, pages 326-330, XP002004457 YAMADA, S. ET AL.: "ALPHA-Adrenoceptors in Human Prostate : Characterisation and Alteration in Benign Prostatic Hypertrophy" see the whole document ---	1-14
Y	WO,A,94 10989 (SYNAPTIC PHARMA CORP ;GLUCHOWSKI CHARLES (US); FORRAY CARLOS C (US) 26 May 1994 see the whole document ---	1-14
Y	DRUG DEVELOPMENT RES., vol. 28, 1993, pages 56-64, XP002005338 GIARDINA, W.J. ET AL.: "A-75169 HCl: Pharmacological Profile and Ocular Pharmacology Studies of a New alpha-2 Antagonist " see the whole document ---	1-14
Y	BIOORG.&MED.CHEM.LETT., vol. 3, no. 4, 1993, OXFORD, pages 561-564, XP002004458 LAWSON, J.E. ET AL. : "Preparation and in vitro Biological Evaluation of the Enantiomers of the Dihydropyridine BM 20014, a combination calcium and alpha-1-Adrenoreceptor Antagonist " see the whole document -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/00178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO-A-9312754	08-07-93	US-A-	5288749	22-02-94
		AU-B-	3278993	28-07-93
		CA-A-	2125392	08-07-93
		EP-A-	0646112	05-04-95

EP-A-0095666	07-12-83	AU-B-	560459	09-04-87
		AU-B-	1445283	08-12-83
		CA-A-	1215376	16-12-86
		JP-C-	1760125	20-05-93
		JP-B-	4043064	15-07-92
		JP-A-	58225064	27-12-83
		US-A-	4618683	21-10-86

WO-A-8906645	27-07-89	CA-A-	1337425	24-10-95
		DE-D-	68909253	28-10-93
		DE-T-	68909253	24-02-94
		EP-A,B	0325963	02-08-89
		EP-A-	0395734	07-11-90
		ES-T-	2059570	16-11-94
		JP-T-	4500356	23-01-92
		US-A-	5128362	07-07-92
		US-A-	5086074	04-02-92
		US-A-	5140040	18-08-92

WO-A-8906534	27-07-89	DE-T-	68908392	10-02-94
		EP-A-	0325964	02-08-89
		EP-A,B	0396620	14-11-90
		ES-T-	2059828	16-11-94
		JP-T-	3502325	30-05-91
		US-A-	5089519	18-02-92
		US-A-	5140039	18-08-92
US-A-	5185364	09-02-93		

EP-A-0325963	02-08-89	CA-A-	1337425	24-10-95
		DE-D-	68909253	28-10-93
		DE-T-	68909253	24-02-94
		EP-A-	0395734	07-11-90
		ES-T-	2059570	16-11-94
		JP-T-	4500356	23-01-92
		WO-A-	8906645	27-07-89

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/00178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0325963		US-A- 5128362	07-07-92
		US-A- 5086074	04-02-92
		US-A- 5140040	18-08-92

US-A-5158953	27-10-92	EP-A- 0594883	04-05-94
		US-A- 5512677	30-04-96
		US-A- 5340814	23-08-94

WO-A-9410989	26-05-94	US-A- 5403847	04-04-95
		AU-B- 5602994	08-06-94
		CA-A- 2148839	26-05-94
		EP-A- 0667769	23-08-95
		US-A- 5508306	16-04-96
		ZA-A- 9308510	02-08-94
